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Defining outcomes following Congenital Diaphragmatic Hernia using Standardised Clinical Assessment and Management Plan (SCAMP) methodology within the CDH EURO Consortium

Running title: SCAMP for follow-up of CDH

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Regular Review

Abstract

Treatment modalities for neonates born with congenital diaphragmatic hernia (CDH) have greatly improved in recent times with a concomitant increase in survival. In 2008, CDH EURO Consortium, a collaboration of large volume CDH centres in Western Europe, was established with a goal to standardise management and facilitate multi-centre research. However, limited knowledge on long-term outcomes restricts identification of optimal care pathways for CDH survivors in adolescence and adulthood. This review is aimed to evaluate the current practice of long-term follow-up within the CDH EURO Consortium centers, and to review the literature on long-term outcomes published from 2000 onwards. Apart from having disease-specific morbidities, children with CDH are at risk for impaired neurodevelopmental problems and failure of educational attainments which may affect participation in society and the quality of life in later years. There is thus every reason to offer them long-term multidisciplinary follow-up programs. We discuss a proposed collaborative project using Standardised Clinical Assessment and Management Plans (SCAMP) methodology to obtain uniform and standardized follow-up of CDH patients at an international level.

Introduction

In 2008, the Section on Surgery and the Committee on the Fetus and Newborn of the American Academy of Pediatrics (AAP) published an overview of the post-hospital discharge long-term sequelae of infants with congenital diaphragmatic hernia (CDH).(1) However, many of these studies were performed several decades ago, in an era before standardized postnatal management was introduced, and most studies focus on outcome in the first years of life.

Meanwhile, the survival rates for neonates born with CDH have increased significantly as management strategies have evolved.(2, 3) The “price of success”, however, appears to be an increase in long-term morbidity. Chronic pulmonary obstruction and pulmonary vascular disease, neurodevelopmental and hearing impairment, gastro-intestinal dysfunction, in addition to late general surgical and orthopaedic complications are increasingly described.(2, 4)

In 2012, Chiu and IJsselstijn reviewed the long-term outcomes of survivors with CDH and reported the results of a web-based survey to evaluate how many of the 60 participating centers in the CDH Study Group had long-term follow-up in place. Of the 22 (37%) centers that responded, structured follow-up was performed in only 16 (73%).(5)

In 2008, a collaboration of large volume CDH centres in Western Europe led to the establishment of the CDH Euro consortium with the goals of standardizing care, and facilitating the conduct of multi-site randomized controlled trials and structured prospective data collection. One of the first developments within the Consortium was the consensus agreement of a standardized postnatal management protocol.(6) This permitted the group to perform the first randomized controlled trial in CDH patients(7), with subsequent revision of the consensus.(8)

Despite the successful efforts to provide standardized care to CDH patients, accurately assessing the impact of such interventions is extremely challenging without having standardized long-term follow-up.(9) Moreover, this lack of knowledge on long-term outcomes will impede optimal care for older CDH survivors.

In 2010, Rathod et al. proposed a novel methodology to aid the rationalisation of clinical management and permit evolution of care pathways.(10) These “Standardised Clinical Assessment and Management Plans” (SCAMPs) are founded on the understanding that most clinical decisions are not necessarily evidence-based, and that there must be provision for flexibility in relation to changing

practice. To inform such a change, however, assessment and management must be tightly structured and standardised, and data collected using clearly defined unambiguous treatment algorithms. This permits the exploration of hypotheses which are embedded a priori. As CDH is a rare disease, multicentre collaboration is mandatory to apply the SCAMP methodology successfully. We hypothesized that initiation of SCAMPs would be possible within the framework of the CDH EURO Consortium.

The aims of this study were 1) to evaluate the current practice of long-term follow-up within the CDH EURO Consortium centers, 2) to review literature by system on outcomes in CDH published from 2000 onwards, and 3) to discuss SCAMP methodology as a potential approach to obtain uniform and standardized follow-up of CDH patients.

Methods

Survey

We developed a two-part web-based questionnaire. Part 1 aimed at gathering background information and understanding broadly the follow-up practices in participating centers. Part 2 aimed specifically at understanding the current follow-up practice in those centers with a structured CDH follow-up program. One representative from each of the 20 participating centers was contacted by e-mail and invited to co-ordinate completion of the survey on behalf of their institution. The survey was deliberately concise with both multiple choice and open-ended questions. It was unanimously approved at a meeting of the follow-up working group within the CDH EURO Consortium in April 2016.

Literature review

We defined, by consensus, seven areas of interest with respect to long-term morbidities: pulmonary function, pulmonary hypertension (PH), neurodevelopment, sensorineural hearing loss (SNHL), growth and gastrointestinal morbidities, general surgical outcomes and musculoskeletal outcomes. We conducted an extensive literature search from 2000 onwards (Supplementary File S1). Since the main goal of the literature review was to explore unanswered questions we decided not to use the systematic literature review methodology. Based on title and abstract, articles were categorized and included for evaluation. Members of the working group, focusing on their area of expertise, summarized the current knowledge base in predefined tables delineating the most important issues.

Results

Survey

Nineteen centers answered the first part of the survey in its entirety (95%). Among the respondents were nine neonatologists (47%), seven pediatric surgeons (37%), one pediatrician (5%), one pediatric intensivist (5%), and one obstetrician (5%). The annual case volume of responding centers is shown in Figure 1.

All centers reported that CDH patients were followed up at their institution, however, 4/19 (21%) respondents reported that follow-up was not structured and standardized. Two centers discontinued structured follow-up at 1 year of age. The reasons provided were: lack of resources or personnel, or a large catchment area.

Three centers (16%) endorsed following up all CDH patients routinely, whereas 16 centers (84%) supported review of only those at highest risk of morbidity. The presence of chronic lung disease was selected as the most important risk factor (94%; Table 1). All respondents unanimously agreed and endorsed standardization of follow-up and were willing to adopt such a collectively agreed pathway within the EURO Consortium.

Fifteen participating centers answered the second part of the survey (79%); 13 provided follow-up standardized both for time points and data collection (87%), the remainder (13%) for time points alone. A summary of the follow-up services currently provided is shown in Table 2. None of the centers performed annual follow-up until 16 years of age; only one center offered annual review until 10 years of age. Only half of the centers performed follow-up after the age of 12 years (Table 2). For the 5 centers that provided follow-up until 16-20 years, the time intervals between reviews were usually 3-6 months within the first two years of life, with wider intervals of up to 2-6 years once school aged.

Pulmonary assessments

In 11 centers (73%) chest radiographs were performed routinely in every CDH patient; in 5 of those (33%) within the first year of life only. In three centers (20%) follow-up chest radiographs were taken routinely but restricted to CDH patients repaired with a patch. One center that applied pH-metry routinely at 0.5 and 8 years carried out chest radiographs for assessing tube position and

diaphragmatic integrity. One center which offered fetal tracheal occlusion, performed a chest CT routinely at one year of age. One center performed chest MRIs routinely at 2 and 10 years of age. Two centers performed routine pulmonary function testing within the first year of life; in 5 other centers, pulmonary function testing was done in childhood. One center discontinued pulmonary function testing after the age of 6 years, whereas the 4 other centers performed repeated measurements at 4-5 year intervals at older ages.

Cardiac assessments

Four centers performed routine echocardiograms within the first year of life irrespective of the presence of pulmonary hypertension prior to discharge. In one of those centers, evaluations at 5 and 12 years were scheduled for those with pulmonary hypertension identified at 1 year. One other center restricted routine echocardiograms to those with chronic pulmonary hypertension. Two centers evaluated pulmonary hypertension at 14 or 16 years; one of these centers provided routine echocardiograms every 2 to 4 years after the age of 2 years.

Neuro-imaging and neurodevelopmental assessments

Only one center provided routine cranial MRI (at 2 and 10 years). Hearing assessments were offered routinely after discharge in 6/19 centers (32%); two centers performed hearing assessments after the age of 5 years. One center offered hearing assessments every 6 months until 6 years of age. Routine neurodevelopmental assessments were performed until 2 years in half of the participating centers; in 5/19 centers (26%) it was carried out until 5 years of age. Two centers offered routine neuropsychological assessments after 5-6 years of age.

Anthropometry and gastro-intestinal studies

All participating centers evaluated height and weight at each assessment. Upper gastrointestinal studies to evaluate reflux were routinely performed after discharge in 6/19 (32%) centers; one center did this at school age (8 years). Esophagoscopy was offered in one center prior to discharge. A single center reported screening for oral aversion at each hospital visit.

Other investigations

Specific orthopedic assessment for chest wall deformities was reported by two centers.

We now present the literature review on these long-term morbidities in CDH survivors.

Literature review

Pulmonary function

A literature overview is provided in Supplementary Table S1. Follow-up studies assessing pulmonary symptoms in CDH have yielded conflicting results. Wheeze and recurrent cough are reported in approximately 10-50% of pre-school children.(11-14) Asthma appears to be more prevalent in survivors and is reflective of malformation severity.(15, 16) Symptoms of obstructive airways appear to abate with age despite persistence of airflow obstruction on objective measurement.(17) . Indeed, those assessed at mid (4.5±1.8years) and long-term (21±5.7 years) by Arena et al, reported, no respiratory symptoms.(17)

CDH survivors have been reported to suffer from recurrent respiratory tract infections(15, 18), but whether this is greater than in other term born, ventilated infants is unclear. Respiratory syncytial virus (RSV) infection may be severe in CDH patients necessitating hospitalisation and sometimes further surgery.(18) Pneumonia has been reported in 7% of CDH patients during infancy both due to infection and aspiration.(1)

Regarding functional residual capacity (FRC) in infancy, reduced, normal and even increased FRC are reported.The latter reflecting compensatory over-inflation of the contralateral lung.(19-21) Additionally, lower tidal volume, higher resistance and lower compliance of the respiratory system are reported in infancy.(21-23) Conversely, persistent obstructive and restrictive abnormalities are described in older children.(24-28) At eight years of age, CDH survivors had comparatively lower forced vital capacity (FVC), forced expiratory volume at one second (FEV_1) and mean forced expiratory flow between 25% and 75% of the FVC (FEF_{25-75}).(28) In another study, at eight years of age the majority had normal lung function (27) whereas at 11.9 years lower FEV_1, FVC and FEV_1/FVC results were reported.(26) Twenty-six CDH adolescents and 30 controls born between 1985-1991 (mean age of 13 years at follow-up) demonstrated significant differences in FEV_1, FEF_{25-75}, FRC, residual volume/total lung capacity (RV/TLC) and maximal voluntary ventilation (MVV) and reduced muscle strength. A correlation between lung function results and body mass index has been reported.(16, 29) At a mean age of 24.3 years 12 young people had a lower FEV_1, although their quality of life was comparable to the general population.(30) Hyperpolarised 3He magnetic resonance (3HeMR) and anatomical 1H magnetic resonance imaging (1HMRI) studies in those 28 years of age have shown functional changes persist into adulthood.(31)

Opt-electronic plethysmography in 14 children demonstrated significant thoraco-abdominal and trans-thoracic asynchrony and a marked asymmetry in the expansion of the pulmonary rib cage. In those who had a patch repair, the overall diaphragmatic contribution to breathing was significantly reduced.(32)

Ninety-eight patients aged between 11 days and 44 months had pulmonary function testing between one and five occasions using the raised volume rapid compression technique. Forced expiratory flows were below normal and residual volumes and FRCs were elevated.(19) In another series, there was catch up of lung volume, but airflow remained significantly reduced. In 27 CDH and 30 controls (mean age 26.8 years at last follow-up), a longitudinal study demonstrated mild deterioration in airflow obstruction and diffusion capacity since 11.8 years.(33)

Reduced exercise performance is reported in CDH survivors, but may improve with increasing age. At five years of age CDH patients had reduced FEV_1 and maximal exercise performance.(34) Exercise testing at seven years revealed lower anaerobic exercise capacity in CDH children than controls. Self-reports on daily activities may identify CDH survivors with low maximum peak oxygen consumption and thus identify those who may benefit from physical training.(35) In one study, 10-16 year old survivors born in 1985-1991 had mildly reduced exercise capacity, although cardiorespiratory response to exertion was similar to controls.(36) Amongst 27 CDH and 30 controls treated for neonatal respiratory failure all born at term, similar levels of exercise capacity, daily activity and fatigue were seen at a mean age of 26.8 years.(37) Whether reduced exercise capacity impacts unfavourably remains controversial. At 6.6 years, those CDH children who had a higher level of exercise performance had less perception of dyspnoea and effort.(38)

Ventilation perfusion of the ipsilateral lung has been reported in those with pulmonary morbidity and lower body weight at one and two years of age.(39) Sixty-one percent of 46 patients who had at least two scans at a mean age of 1.3 years and 6.3 years had abnormal scans.(40) (15). An association between patch repair and V/Q mismatch has been reported.(25, 40)

Pulmonary hypertension

The incidence and course of PH in children after CDH repair has been studied in a limited number of observational studies (Supplementary Table S2). The underlying pathophysiology and natural history

of PH in CDH are not well understood. Although a number of mediators of smooth muscle tone and vascular development have been identified (nitric oxide-VEGF pathway, endothelin and prostacyclin pathways), subclassification based on these, or other criteria, is not currently possible. There are no agreed standards to stratify PH in CDH *per se*. A variety of stratifications have been employed, based on echocardiographic assessment of pulmonary arterial pressures (PAP).(27, 41-45)

Whether the functional and structural abnormalities of the pulmonary vasculature at birth improve or deteriorate through childhood and beyond is unknown. Observational studies with small numbers of patients have assessed PAP and cardiac function in childhood survivors. At three weeks of age 51% of cases had a PAP of at least half systemic blood pressure.(46) In another study the median age of "resolution" of PH in infants with CDH was 14 (7-21) days with moderate or severe PH in 11% at discharge.(41) Behrsin and coworkers reported that 17% of infants with repaired CDH were discharged on sildenafil.(47) Approximately 40% of CDH survivors are reported to have echocardiographic evidence of PH in the first 3 years of life.(42) Echocardiographic studies in older survivors (6-11 years) have not observed raised PAP.(25, 27) However, evidence of RV dysfunction has been observed at 7 years of age.(43) Cardiac catheterisation studies have demonstrated elevated pulmonary vascular resistance and PAP in CDH survivors up to 12 years of age.(42, 48) Although these studies suggest that chronic PH can occur after CDH repair, they are limited by study size, variation in treatment eras, and illness severity. They also highlight the current lack of standardised definitions of PH, diagnostic techniques, and prospective multi-centre data collection.

Neurodevelopment

Despite arguably creating the greatest patient burden, neurodevelopmental morbidity from CDH has, until recently been under-reported due to limited follow-up. Additionally, standardized assessments cannot be performed in children with severe disabilities. A literature overview is provided in Supplementary Table S3.

From infancy until school age, normal scores for cognition have been reported in CDH survivors. Overall, the cognitive and language development scores at preschool age are normal to mildly delayed(9, 49-54)with ECMO exposure an independent predictor of impaired mental development.(50, 52, 55)

The findings across published studies are difficult to compare because of variability in age at assessment and study design. In CDH survivors Danzer(56) reported that 44% of infants had mild, and 13% severe neurodevelopmental delays in at least one domain at 1 year of age. Benjamin reported that 44% were at risk for neurocognitive delay at median age of 4.9 years.(57)

At school age, intelligence appears in the average range.(58-63) with only a single Japanese study reporting overall low intelligence in a cross-sectional cohort of 6-17 year-olds.(64) Despite overall average cognition, many children (up to 50%) struggle in standard educational programs.(63) By school age survivors also experience concentration/attention problems.(59, 63) ECMO-treated CDH patients have significantly lower scores on visual motor integration compared with neonatal ECMO controls.(62) Other studies report normal(59) to slightly impaired scores(55, 58) on visual motor integration. The children report that their perception of general health is reduced when compared to the reference norm(65, 66), positively they report a well-developed feeling of self-confidence.(63, 66) Such neurocognitive delays recorded in earlier life may improve.(55)

Data on motor function in children with CDH is scarce, but problems occur in approximately 40% of children at preschool age and 20-30% at school age. Preschool motor development scores in CDH patients are usually reported to be normal or subnormal(9, 49, 51-53, 55, 61, 67) seeming to improve between 1 and 3 years of age.(51, 53) In a population of 47 CDH patients of whom 26% received ECMO, mild to severe motor function delay was reported in 45% and 19% at 1 and 3 years, respectively.(51) At 5 years 47% of ECMO-treated CDH patients had normal motor function; the remaining 53% had gross delays.(60) In another study, 58% of 5-year-olds, both with and without need for ECMO, had normal motor function.(68) In a cross-sectional cohort of 15 non-ECMO treated CDH-patients aged 6-15 years old Tureczek and co-workers observed gross motor function problems in 80%, whereas motor performance was normal in all 8 participants aged 3-5 years in the same study.(61) Although motor function seems to improve at the age of 8 years(63, 69), it deteriorates when the children get older.(69) This suggests that CDH patients grow into their deficits when tasks become more complex.

Sensorineural hearing loss

SNHL is the most common sensory deficit in humans with a prevalence ranging from 1.5 to 6.0 per 1000 live births(70) with a tenfold higher prevalence (1% to 3%) in those who require neonatal intensive care.(71) A literature overview is provided in Supplementary Table S4.

In patients with CDH, SNHL has been reported with a variable prevalence, ranging from 0%(72) to 100%.(73) Although earlier studies tend to present a higher prevalence of SNHL, Amoils and co-workers report a prevalence of SNHL over 50% in 2015.(74) Controversies exist on the impact of the diagnosis of CDH on the risk of SNHL development. In a study on 111 ECMO graduates, Fligor and co-workers reported a 26% overall prevalence of SNHL in neonates with severe respiratory distress and described CDH as an independent risk factor.(75) Conversely, a more recent study of 136 ECMO survivors observed a prevalence of 9% of SNHL, irrespective of the underlying diagnosis.(76) As far as the natural history is concerned, in CDH patients SNHL tends to present as late-onset and progressive. Most studies with data from neonatal hearing screening, report normal findings.(73, 74, 77-81) Therefore, the extreme variability in length of follow-up in available reports, precludes firm conclusions on the actual prevalence.

The most frequently reported factors associated with SNHL are ECMO treatment(74, 75, 82, 83), length of mechanical ventilation and/or stay in the NICU or in hospital(74, 78, 79, 83-85), need for inhaled nitric oxide(84), patch repair(74), and dose and duration of specified drugs: loop diuretics(74, 78, 82-84), aminoglycosides(75, 83, 84) and pancuronium bromide(78, 84) Overall, these factors suggest that the most critically ill CDH patients are at greatest risk. Identifying definite factors that place CDH patients at high risk for SNHL will permit their modification and may aid prognostication.

Gastrointestinal morbidity and growth

CDH related gastrointestinal morbidity is common.(86) The main morbidities are oral aversion (OA), need for tube feeding (NFT), failure to thrive (FTT), and gastro-esophageal reflux disease (GERD) (Supplementary Table S5).

Slower growth velocity in infants with CDH during the early postnatal period is described.(22) Approximately 20-30% experience FTT within the first years of life which may persist into adolescence.(87, 88) However, Gien and coworkers revealed the highest risk for comorbidities at both extremes of growth velocity.(89) Leeuwen and co-workers observed stunting and wasting up to 12

years of age, although growth failure became less prevalent after correcting for individual target height.(88) Several risk factors expressing the severity of CDH have been identified: the intensity of respiratory support, ECMO use, and oxygen supplementation at discharge.(90-92) Data about the underlying mechanism for FTT in CDH are scarce. Increased work of breathing, OA, GERD and acute metabolic stress have been identified as contributing factors.(93-95)

A recent study demonstrated that 58% of infants with CDH were in a hypermetabolic state measured by indirect calorimetry supporting the need for increased caloric intake for appropriate growth.(90) The best nutritional strategy for these infants is uncertain and an individually tailored approach is generally used. The optimal growth targets for this population remain unidentified, and whether a strategy of hyperalimentation risks later cardiovascular disease.(96)

GER is present in up to 86% of infants with CDH in the first year of life.(97) Ascertaining whether GER is pathologic or not is a key.issue. Identified risk factors include: antenatal diagnosis, intrathoracic liver position, patch closure, stomach position, esophageal dysmotility and tube feeding at discharge.(98-100) Gastrointestinal symptoms (GERD, FTT, OA) are associated with a longer hospital course, prolonged mechanical ventilation and a longer need for parenteral nutrition.(101) The diagnostic approach for suspected GERD in infants with CDH should be based on standard guidelines.(102) Therapeutic approaches include proton pump inhibitors and surgical fundoplication. In one study the need for anti-reflux surgery related to gestational age and defect size.(101) Not all infants demonstrate improvement in anthropometric scores following treatment.(87) GERD can lead to worsening of chronic lung disease, aspiration pneumonia, malnutrition and FTT. Its presence has an effect on quality of life.(16) There are a few studies on primary anti-reflux surgery and its effect on growth and GERD with conflicting results.(101, 103) Patients without prophylactic antireflux surgery typically undergo this treatment before 6 months of age.(104) The long term outcome of GERD in CDH patients is unclear. However, Barrett's esophagus and esophageal adenocarcinoma have been described in CDH patients.(105)

The reported incidence of OA is as high as 25%; the underlying etiology is largely unknown.(16, 72) It has been suggested that the endotracheal tube might interfere with the development of a normal swallow .(94) The incidence of OA in patients with CDH is associated with a more severe postnatal clinical course. Early aggressive intervention failed to reduce its incidence.

NTF is described in association with FTT in CDH patients. Data on its use are scarce with a reported incidence between 18 and 70%, and an association with markers of disease severity.(13, 90, 93)

General surgical morbidity

Long-term general surgical morbidities include recurrence of the diaphragmatic defect, chronic patch infections, and volvulus in those with rotational anomalies (Supplementary Table S6).

All literature reports identified were retrospective, mostly single centre and with variable follow-up time points. Hence, comparison across studies is not feasible. Small defects (A and most of B according to the CDH Study Group Staging System(106) are closed primarily by direct non-absorbable sutures. In large defects (large B, C or D) a patch is typically employed. The risk for recurrence relates to closure technique – which are not standardised (107-112), liver position(113), and patch material.(112) Minimally invasive surgery (MIS) has become more common, with a corresponding increase in recurrence rates.(108, 114, 115) Up to 2/3 of recurrences are found incidentally. Plain x-ray does not have a high sensitivity for detecting recurrences, but remains the most commonly used diagnostic tool.

The incidence of small bowel obstruction may be higher with patch closure (113) but reports are contradictory.(110) A MIS approach may be protective.(116)

Infectious complications are seldom encountered and conservative therapy with antibiotics seems to be appropriate.(110)

Data on malrotation management and need for follow-up in children with CDH are lacking. Only two studies report on volvulus(109, 117) with a prevalence of 0.3% when no Ladd's procedure was performed.(117)

Musculoskeletal morbidity

Until recently there have been few reports on musculoskeletal morbidity in CDH patients (Supplementary Table S7). Whereas the prevalence of idiopathic scoliosis at school age is approximately 0.5%(118), it was reported in 2 to 26% in children with CDH. However, application of the more restrictive current definition of scoliosis results in a lower prevalence. Whereas, Kuklova and coworkers showed no impact of closure technique(119), Russell reported the prevalence of sciolosis

following muscle flap or patch repair to be twice that of those following primary closure (13, 15 and 7%, respectively).(120) Jancelewicz and coworkers noted scoliosis in 10% of children who underwent non-primary repair.(109)

Chest wall deformity (i.e. pectus excavatum) occurs in 4-50% of patients (Supplementary Table S7) and may relate to defect size and closure technique.(119, 120) Jancelewicz et al. reported that mild chest deformity was extremely common at all ages, but major deformity requiring referral and eventually further treatment occurred in only 8% of patients and at a median age of 5 (range 1.1–6.8) years.(108)

Discussion:

We aimed to evaluate the current practice of long-term follow-up within the CDH EURO Consortium centers and to review the literature informing such activity. All respondents agreed that standardization of follow-up was needed and were willing to adopt a collectively agreed standardized follow-up pathway within the Consortium. Although, follow-up was structured and standardized in 15 of 19 participating centers, only three centers supported following up *all* CDH patients without any risk stratification. The majority of centers supported review of only those at highest risk of morbidity. Lack of resources or personnel were identified as the most important barriers to implementing a structured follow-up programme.

Literature review showed that children with CDH suffer from substantial long-term morbidity across several domains. However, most data arises from retrospective chart reviews, usually from single centres of small series of patients and the proportion of eligible patients is frequently low or unknown. In short, the current literature is insufficient to provide clear guidance on what constitutes ideal follow-up of children with CDH.

To optimize long-term care with standardized follow-up for children with CDH, a task force of members of the CDH EURO Consortium agreed to use the Standardized Clinical Assessment and Management Plans (SCAMP) methodology to establish care pathways. SCAMPs outline a data-backed, consensus-based, care pathway for a diverse patient population with a particular diagnosis or condition.(121) The methodology aims at improving patient outcomes, reduce practice variation, and reduce unnecessary resource utilization. Assessment of the effectiveness of diagnostic testing and

management interventions is included in the process.(10, 121) This approach, which has been used extensively in health care since its introduction in 2009(122), may - in the long run - reduce the burden of lack of resources or personnel to perform standardised follow-up. Moreover, it may contribute to standardisation of assessments facilitating international multicentre collaboration.(9)The first step in the process - which includes formulation of a background position paper based on literature review and evaluation of current practice(121, 122) - has been undertaken by the CDH EURO Consortium members (Figure 2). This step will be followed by definition of plausible outcomes (closely specified statements potentially refutable by accumulating and reviewing unbiased follow-up data), identification of entry criteria, and assessment and recommended management algorithms. Thereafter, targeted data collection, recorded on SCAMP data forms will followed by iterative data analysis enabling modification of the follow-up algorithms.(10, 122) This process will be labor intensive and require careful thought. We expect that this initiative will stimulate multicenter collaboration within the Consortium and lead to the evidence-based provision of long-term multidisciplinary care for CDH patients, and ultimately improved clinical outcomes. With increased survival rates after introduction of standardized treatment protocols for CDH patients(3), more children will reach adulthood and participate in society. Recommendations for optimal multidisciplinary follow-up are expected to disseminate into adult care.

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Figure legends

Figure 1:

Current practice of structured and standardized follow-up in 19 CDH centers stratified for the number of new CDH cases treated annually.

The x-axis represents the stratification for new CDH cases treated annually per center; the y-axis represents the number of centers.

Figure 2:

Standardised Clinical Assessment and Management Plan (SCAMP) proposal for long-term follow-up in congenital diaphragmatic hernia (CDH).

Figure based on the schematic representation of SCAMPs (solid boxes) proposed by Rathod and coworkers.(10) Steps that still need to taken are indicated in italics. a: By consensus seven domains of interest were selected: pulmonary morbidity, pulmonary hypertension, neurodevelopmental morbidity, sensorineural hearing loss, gastrointestinal morbidity and growth, surgical morbidity and musculoskeletal morbidity; b: To explore the feasibility of development of SCAMP and performing assessments within the CDH EURO Consortium we performed a survey on current practices of follow-up of CDH patients (dashed box); c: Multiple plausible outcomes based on literature review of seven domains and involvement of patient support groups will be explored simultaneously; d: capture and explore deviations(10); e: iterative data analysis and SCAMP modification(10).

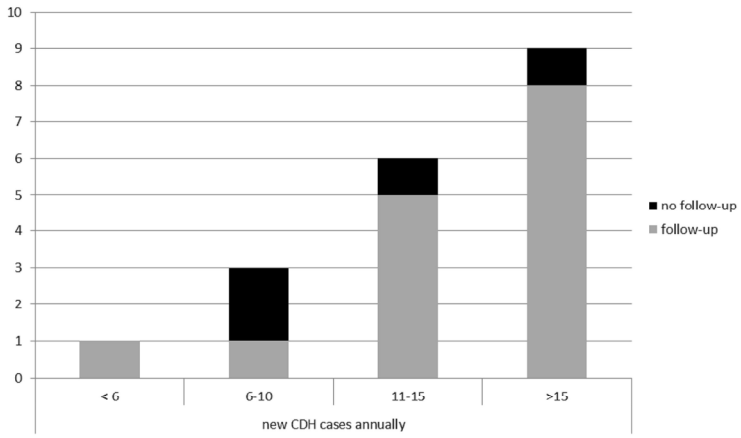
Table 1: Factors suggested for risk stratification of long-term follow-up in CDH patients

Risk factors	
Chronic lung disease	16 (94%)
Feeding difficulties or growth problems	14 (82%)
Neurologic morbidity	13 (74%)
Need for ECMO	11 (65%)
Mode of closure / use of patch	10 (59%)
Gastrointestinal issues	9 (53%)
Observed/expected lung-to-head ratio	4 (24%)
Pulmonary hypertension / ICU issues	1 (6%)

Multiple options were applicable; this question was answered by 17 participants, two centers that provide a uniform follow-up program for all CDH patients replied that risk stratification was not applicable. Data are shown as n (%). ECMO = extra corporeal membrane oxygenation

Table 2: Follow-up programs provided within the CDH EURO Consortium centers

Age of follow-up	infancy	15 (100%)
	toddler	13 (87%)
	(pre)school	13 (87%)
	adolescence (>12 yrs)	8 (53%)
	up till 20 yrs	1 (7%)
Disciplines involved	pediatric surgeon	14 (93%)
	pediatrician	11 (73%)
	pulmonologist	11 (73%)
	pediatric physical therapist	6 (40%)
	dietician	5 (33%)
	pediatric cardiologist	5 (33%)
	speech-language pathologist	4 (27%)
	psychologist	3 (20%)
	neonatologist	2 (13%)
	orthopedic surgeon	1 (7%)
	clinical geneticist	1 (7%)
Assessments performed	anthropometry (height, weight)	15 (100%)
	chest radiograph	11 (73%)
	gastroesophageal reflux	11 (73%)
	pulmonary function	10 (67%)
	mental development	8 (53%)
	motor function development	8 (53%)
	audiometry	8 (53%)
	echocardiography	6 (40%)
	maximal exercise test	5 (33%)
	social-emotional wellbeing	4 (27%)
	extensive neuropsychological testing	3 (20%)
	electrocardiogram	3 (20%)
	quality of life assessment	3 (20%)
	intracranial imaging ultrasound	3 (20%)
	orthopedic assessment	2 (13%)
	CT chest	1 (7%)
	ventilation/perfusion scan	1 (7%)
	intracranial imaging MRI	1 (7%)
	thoracic MRI	1 (7%)
	genetic assessment	1 (7%)
	cardiac catheterization	0



Current practice of structured and standardized follow-up in 19 CDH centers stratified for the number of new CDH cases treated annually.

The x-axis represents the stratification for new CDH cases treated annually per center; the y-axis represents the number of centers.

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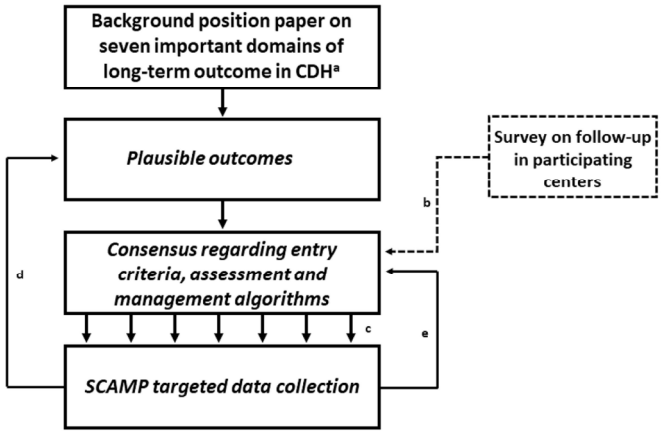

Standardised Clinical Assessment and Management Plan (SCAMP) proposal for long-term follow-up in congenital diaphragmatic hernia (CDH).
Figure based on the schematic representation of SCAMPs (solid boxes) proposed by Rathod and coworkers.(10) Steps that still need to taken are indicated in italics. a: By consensus seven domains of interest were selected: pulmonary morbidity, pulmonary hypertension, neurodevelopmental morbidity, sensorineural hearing loss, gastrointestinal morbidity and growth, surgical morbidity and musculoskeletal morbidity; b: To explore the feasibility of development of SCAMP and performing assessments within the CDH EURO Consortium we performed a survey on current practices of follow-up of CDH patients (dashed box); c: Multiple plausible outcomes based on literature review of seven domains and involvement of patient support groups will be explored simultaneously; d: capture and explore deviations(10); e: iterative data analysis and SCAMP modification(10).

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Methodology

Two-step approach: First, authors of the respective sections of the background position paper performed literature searches using disease-specific keywords in Medline. Searches were limited to publications published after 2000. In addition, an extensive systematic literature search was performed on March 6, 2017 in four different databases: Embase, Medline Ovid, Web of Science and Google Scholar. This systematic literature search revealed in total 1695 hits. After exclusion of publications before 2000 1295 remained; 1132 of them were excluded based on title/abstract after review by one author (H.IJ.). The abstracts of remaining publications were evaluated and based on the reported results the publications were classified to be included in the respective domains of long-term follow-up (i.e. pulmonary morbidity, pulmonary hypertension, neurodevelopment, SNHL, growth and gastrointestinal morbidity, surgical morbidity and musculoskeletal morbidity). Then, the authors of the respective chapters reviewed the results of the systematic search and added references if deemed appropriate.

Embase.com	1273	1257
Medline Ovid	883	163
Web of science	760	179
Google scholar	200	96
Total	**3116**	**1421**

Embase.com 1273

('congenital diaphragm hernia'/exp OR ('congenital malformation'/de AND 'diaphragm hernia'/de) OR 'Bochdalek hernia'/de OR ((congenital* NEAR/6 diaphragm* NEAR/6 (herni* or defect* OR problem*)) OR ((Morgagni* OR bochdalek*) NEAR/3 herni*)):ab,ti) AND ('lung function'/exp OR 'respiratory function'/exp OR 'lung function test'/exp OR 'lung disease'/de OR 'lung hypoplasia'/de OR 'exercise test'/exp OR 'pulmonary hypertension'/de OR 'persistent pulmonary hypertension'/de OR 'heart function'/exp OR 'echocardiography'/exp OR 'heart catheterization'/exp OR 'mental disease'/de OR 'mental development'/exp OR 'mental development assessment'/exp OR 'intelligence'/exp OR 'motor performance'/exp OR 'motor function test'/exp OR 'hearing disorder'/exp OR 'growth'/de OR 'body mass'/de OR 'body size'/de OR 'body weight'/de OR 'digestive system function disorder'/exp OR 'feeding difficulty'/exp OR 'recurrent disease'/de OR 'intestine volvulus'/exp OR 'intestine obstruction'/exp OR 'malrotation syndrome'/exp OR 'postoperative complication'/de OR 'musculoskeletal system'/de OR 'bone'/exp OR muscle/exp OR 'scoliosis'/de OR 'gastrointestinal symptom'/exp OR 'lung volume'/exp OR 'chronic lung disease'/de OR (((lung OR pulmonar* OR respirat* OR heart OR cardiac* OR cardial* OR cardiol* OR cardiopulmon*) NEAR/3 (function* OR dysfunction* OR test* OR outcome* OR morbidit* OR hypertens* OR pressure*)) OR (exercise NEAR/3 (capacit* OR perform* OR Toleran* OR test*)) OR ((chronic* OR longterm* OR long-term*) NEAR/3 oxygen*) OR echocardiogra* OR ((heart OR cardiac*) NEAR/3 catheter*) OR neurodevelopment* OR ((mental* OR cogniti* OR psychomotor* OR motor OR speech* OR language* OR verbal* OR hearing OR auditor* OR development* OR neuromuscul* OR neurobehav* OR neurological* OR functional*) NEAR/3 (outcome* OR development* OR performan* OR skill* OR

function* OR dysfunction* OR loss OR disorder* OR test* OR assess*)) OR intelligen* OR intellect* OR (body NEAR/3 (weight OR mass OR size OR height)) OR digestive OR reflux OR gastrointestin* OR gastro-intestin* OR gastroesophag* OR gastro-esophag* OR gastroaesophag* OR gastro-aesophag* OR feeding OR eating OR (intest* NEAR/3 (adhesion* OR obstruct*)) OR ((surg* OR postsurg* OR postop* OR operati*) NEAR/3 (morbid* OR complicat*)) OR recurr* OR relaps* OR volvul* OR (small* NEAR/6 (intestin* OR bowel*) NEAR/6 obstruct*) OR malrotat* OR musculoskelet* OR skelet* OR scoliosis OR muscle* OR (pulmonar* NEAR/3 (hypoplas* OR resistan*)) OR ((lung OR pulmonar*) NEAR/3 (volume* OR chronic*))):ab,ti) AND ('survivor'/de OR child/de OR 'infant'/de OR 'school child'/de OR adult/exp OR (survivor* OR child* OR schoolchild* OR infan* OR adult* OR long-term* OR longterm*):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim AND ('cohort analysis'/exp OR 'follow up'/exp OR 'retrospective study'/exp OR 'prospective study'/exp OR 'longitudinal study'/exp OR 'controlled study'/exp OR 'major clinical study'/de OR 'outcomes research'/de OR (cohort* OR 'follow up' OR followup OR retrospectiv* OR prospectiv* OR longitudinal* OR control*):ab,ti)

Medline Ovid 883

("Hernias, Diaphragmatic, Congenital"/ OR ("Congenital Abnormalities"/ AND "Hernia, Diaphragmatic"/) OR ((congenital* ADJ6 diaphragm* ADJ6 (herni* or defect* OR problem*)) OR ((Morgagni* OR bochdalek*) ADJ3 herni*)).ab,ti,kf.) AND ("Respiratory Function Tests"/ OR "Lung Diseases"/ OR "exercise test"/ OR "Hypertension, Pulmonary"/ OR "Heart Function Tests"/ OR exp "echocardiography"/ OR "Cardiac Catheterization"/ OR "Mental Disorders"/ OR "Neurobehavioral Manifestations"/ OR "Psychomotor Disorders"/ OR "intelligence"/ OR exp "Psychomotor Performance"/ OR exp "Hearing Disorders"/ OR "Growth and Development"/ OR "Body Weight"/ OR "Body Size"/ OR exp "Gastrointestinal Diseases"/ OR "Feeding and Eating Disorders"/ OR "Recurrence"/ OR "Intestinal Volvulus"/ OR "Intestinal Obstruction"/ OR "Postoperative Complications"/ OR "Musculoskeletal System"/ OR exp "Skeleton"/ OR exp Muscles/ OR "scoliosis"/ OR "Lung Volume Measurements"/OR "Exercise Tolerance"/ OR (((lung OR pulmonar* OR respirat* OR heart OR cardiac* OR cardial* OR cardiol* OR cardiopulmon*) ADJ3 (function* OR dysfunction* OR test* OR outcome* OR morbidit* OR hypertens* OR pressure*)) OR (exercise ADJ3 (capacit* OR perform* OR Toleran* OR test*)) OR ((chronic* OR longterm* OR long-term*) ADJ3 oxygen*) OR echocardiogra* OR ((heart OR cardiac*) ADJ3 catheter*) OR neurodevelopment* OR ((mental* OR cogniti* OR psychomotor* OR motor OR speech* OR language* OR verbal* OR hearing OR auditor* OR development* OR neuromuscul* OR neurobehav* OR neurological* OR functional*) ADJ3 (outcome* OR development* OR performan* OR skill* OR function* OR dysfunction* OR loss OR disorder* OR test* OR assess*)) OR intelligen* OR intellect* OR (body ADJ3 (weight OR mass OR size OR height)) OR digestive OR reflux OR gastrointestin* OR gastro-intestin* OR gastroesophag* OR gastro-esophag* OR gastroaesophag* OR gastro-aesophag* OR feeding OR eating OR (intest* ADJ3 (adhesion* OR obstruct*)) OR ((surg* OR postsurg* OR postop* OR operati*) ADJ3 (morbid* OR complicat*)) OR recurr* OR relaps* OR volvul* OR (small* ADJ6 (intestin* OR bowel*) ADJ6 obstruct*) OR malrotat* OR musculoskelet* OR skelet* OR scoliosis OR muscle* OR (pulmonar* ADJ3 (hypoplas* OR resistan*)) OR ((lung OR pulmonar*) ADJ3 (volume* OR chronic*))).ab,ti,kf.) AND ("survivors"/ OR exp child/ OR "infant"/ OR adult/ OR (survivor* OR child* OR schoolchild* OR infan* OR adult* OR long-term* OR longterm*).ab,ti,kf.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la. AND (exp "Cohort Studies"/ OR "Patient Outcome

Assessment"/ OR (cohort* OR "follow up" OR followup OR retrospectiv* OR prospectiv* OR longitudinal* OR control*).ab,ti,kf.)

Web of science 760

TS=((((congenital* NEAR/5 diaphragm* NEAR/5 (herni* or defect* OR problem*)) OR ((Morgagni* OR bochdalek*) NEAR/2 herni*))) AND ((((lung OR pulmonar* OR respirat* OR heart OR cardiac* OR cardial* OR cardiol* OR cardiopulmon*) NEAR/2 (function* OR dysfunction* OR test* OR outcome* OR morbidit* OR hypertens* OR pressure*)) OR (exercise NEAR/2 (capacit* OR perform* OR Toleran* OR test*)) OR ((chronic* OR longterm* OR long-term*) NEAR/2 oxygen*) OR echocardiogra* OR ((heart OR cardiac*) NEAR/2 catheter*) OR neurodevelopment* OR ((mental* OR cogniti* OR psychomotor* OR motor OR speech* OR language* OR verbal* OR hearing OR auditor* OR development* OR neuromuscul* OR neurobehav* OR neurological* OR functional*) NEAR/2 (outcome* OR development* OR performan* OR skill* OR function* OR dysfunction* OR loss OR disorder* OR test* OR assess*)) OR intelligen* OR intellect* OR (body NEAR/2 (weight OR mass OR size OR height)) OR digestive OR reflux OR gastrointestin* OR gastro-intestin* OR gastroesophag* OR gastro-esophag* OR gastroaesophag* OR gastro-aesophag* OR feeding OR eating OR (intest* NEAR/2 (adhesion* OR obstruct*)) OR ((surg* OR postsurg* OR postop* OR operati*) NEAR/2 (morbid* OR complicat*)) OR recurr* OR relaps* OR volvul* OR (small* NEAR/5 (intestin* OR bowel*) NEAR/5 obstruct*) OR malrotat* OR musculoskelet* OR skelet* OR scoliosis OR muscle* OR (pulmonar* NEAR/2 (hypoplas* OR resistan*)) OR ((lung OR pulmonar*) NEAR/2 (volume* OR chronic*)))) AND ((survivor* OR child* OR schoolchild* OR infan* OR adult* OR long-term* OR longterm*)) AND ((cohort* OR "follow up" OR followup OR retrospectiv* OR prospectiv* OR longitudinal* OR control*))) AND DT=(article) AND LA=(english)

Google scholar

"congenital diaphragm|diaphragmatic hernia" "pulmonary|lung|respiratory|cardiac function|test|outcome"|"mental|cognitive|psychomotor|motor|developmental|functional outcome|development|performance|skills cohort|"follow up"|retrospective|prospective

Supplementary Table S1: Pulmonary morbidity

Reference (population)	Proportion available at FU	Time frame of FU	Main outcome parameters	Outcome description
Muratore, 2001(1) 100 CDH, birth dates not clear	25 (25%) over five years of age performed pulmonary function tests	Retrospective review of a monthly multidisciplinary clinic between 1990-1999	Pulmonary function	28% had obstructive abnormalities
Davis, 2004(2) 73 CDH, born 1991 to 2000	100%	Retrospective chart review 67 months	Survival and outcome	48% had respiratory problems, 59% gastrointestinal problems and 19% severe neurodevelopmental problems
Stefanutti, 2004(3) 24 CDH, born 1985 to 1994	24 of 29 (83%) patients	Cross-sectional 8.15 ± 2.80 years	Chest radiograph ECHO Pulmonary perfusion Scintography Static lung volumes and spirometry	Mean lung function in the normal range, 6/24 (25%) children had a mild restrictive pattern, 3/24 (12.5%) an obstructive pattern and 1/24 a mixed pattern. Mean perfusion to the affected size was significantly lower but on both sides within the normal range
Arena, 2005(4) 31 left-sided CDH without a patch, born 1972 to 2002	31 of 38 (82%) patients To assess pulmonary function and diaphragmatic function	Retrospective, 4.5 and 21 years	Chest x-ray Diaphragmatic ultrasound Pulmonary perfusion scintigraphy	Normal life style – no respiratory symptoms and reduced diaphragmatic mortality
Trachsel, 2005(5) 26 CDH, born 1985 to 1991	26 of 56 (46%) patients	Cross-sectional case-control study, 13 years	Pulmonary function testing and maximum inspiratory and	48% versus 4% of controls showed significant improvement of FEV_1 after bronchodilator

Supplementary Table S1: Pulmonary morbidity

			expiratory pressures	Significant differences in lung function results
Kamata, 2005(6) 33 CDH, born 1986 to 2000	All survived beyond one year without other serious congenital anomalies	Prospective follow up 4.1 ± 2.5 years	Clinical exam Growth parameters ECHO Ventilation and perfusion Scintigraphy	Restrictive abnormalities Five patients had reduced ventilation perfusion
Arena, 2005(4) 10 CDH, born 1972 to 1997	10 of 40 (25%) patients	Cross-sectional, prospective 16 (5-26) years	Diaphragmatic function	Amplitude of contraction was significantly reduced but there was no significant difference between the two sides
Okuyama, 2006(7) 31 CDH, born 1996 to 2002	100%	Prospective, at 1 and 2 years	Physical growth and pulmonary morbidity	VP of the ipsilateral lung lower in those with pulmonary morbidity and lower body weight at one and two years
Trachsel, 2006(8) 1985 to 1991	32 of 56 (57%) patients	Cross-sectional case-control study 10-16 years	Pulmonary function testing and echocardiography	Exercise capacity was mildly reduced in CDH
Koumbourlis, 2006(9) Not clear	Not clear	Retrospective 0-24 months	ILFT: FRC, CRS, RRS, Vmax FRC	All abnormal at 6 months, normalised by 24 months
Peetsold, 2007(10) 12 CDH, born 1960 to 1986	74%	Cross-sectional, prospective 24.3 years	Pulmonary function, diffusion capacity exercise capacity quality of life	Lower FEV_1 FEF_{25-75}, than in the general population Quality of life comparable to the general population
Dotta, 2007(11)	100% of survivors	Longitudinal, 4.5	ILFT: Tidal volumes,	At 4.5 months CDH infants had

Supplementary Table S1: Pulmonary morbidity

13 CDH, born Jan to Dec 2002		and 11.9 months, 28 healthy controls	respiratory rate, tPTEF/Te, CRS, RRS, FRC, LCI	lower tPTEF/Te and RR, RRS and LCI higher At 11.9 months tPTEF/Te lower RRS and LCI higher
Hayward, 2007(12) 46 CDH, born 1990 to 2005	46 of 137 (34%) patients	Retrospective chart review at 3-5 yrs	Abnormal V/Q scans in two or more studies	Patients who underwent a patch repair had nearly seven times the risk of having ipsilateral V/Q mismatch
Basek, 2008(13) 19 CDH, born 1991 to 2001	19 of 30 (63%) patients	Retrospective chart review 7.9 ± 2.8 years	Clinical examination Lung function tests FeNO	47% had one wheezy episode, 21% recurrent wheezy episodes, 47% had lung function impairment. Duration of ventilation nor the length of hospitalisation significantly correlated with lung function. FeNO was within the normal range.
Masumoto, 2008(14) 21 CDH, LHR < 0.2, born 1997 to 2005	Not clear	12 months	RSV infection	5/21 (24%) required RSV hospitalisation
Gischler, 2009(15) 20 CDH (11 ECMO-CDH, 9 non-ECMO CDH), born 1999 to 2003	20 of 22 (91%) patients	Longitudinal, prospective FU 6, 12, 24, 60 months	Pulmonary function and maximal exercise performance	10/20 (50%) developed BPD. Reduced FEV_1 in 25% and maximal exercise in 12.5% at 60 mos.
Roehr, 2009(16) 26 CDH, born – not clear	Not clear	Prospective FU 44 weeks PCA	ILFT: Respiratory rate, tidal volume, FRC, CRS, RRS	Tidal volume was significantly lower, RRS higher, CRS lower
Peetsold, 2009(17) 53 CDH non-	53 of 69 (77%) patients	Cross-sectional 11.9 years	Spirometry Lung volume	CDH survivors had a lower FEV_1, FVC, FEV_1/FVC

Supplementary Table S1: Pulmonary morbidity

ECMO, born 1987 to 1999			Maximal CPET	
Bjorkman, 2011(18) 12 CDH, born 2006 to 2008	Not clear	6 months	SPECT to measure VP distribution, correlation of VP mismatch to neonatal clinical disease severity	Correlation co-efficients were low
Turchetta, 2011(19) 18 CDH (11 active in sport), born 1994 to 2008	Not clear	Cross-sectional 6.6 ± 2.6 years	ECG, maximal exercise stress test, lung function testing	CDH children who were active maintain a higher level of performance with less perception of dyspnoea and effort
Spoel, 2012(20) 43 CDH, born 2004 to 2008	43 of 48 (90%) patients	Longitudinal, prospective, 6 and 12 months	ILFT: Maximum expiratory flow at FRC and FRC	Maximum expiratory flow and FRC were significantly below expected values at 6 and 12 months. Results did not differ according to ECMO status
Prendergast, 2012(21) Born 2006 to 2009	50%	6-24 months	ILFT: FRCpleth, Raw, FRHe, CRS, RRS	CDH infants had higher FRCpleth and lower CRS than those with AWD
Najaf, 2013(22) 22 CDH, born 2006 to 2010	22 of 26 (84%) patients	Retrospective chart review 5 years	?	On discharge 40% had pulmonary problems at follow up
Spoel, 2013(23) 27 non-ECMO CDH, born 1975 to 1986	27 of 40 (68%) patients	Cross-sectional case-control study 26.8 ± 2.9 years	Dynamic and static lung volumes, mid expiratory flows, diffusion capacity	Airflow obstruction and diffusion capacity deteriorated mildly from childhood in survivors of CDH

Supplementary Table S1: Pulmonary morbidity

Wright, 2014(24) 29 CDH, born – not clear	Not clear	Retrospective First 3 years	ILFT: Raised volume Rapid thoraco-abdominal compensation technique and plethysmography	Air flow obstruction in 14 of 29 neonates, 12 obstructive, 9 restrictive
Pantich, 2015(25) born – not clear	Not clear	Prospective lung function 11-44 months	ILFT: Raised volume Rapid thoracic compressions technique	Forced expiratory flows were below normal, particularly in those who required patch closure at ECMO
Healy, 2015(26) 66 CDH (18 with PH), born 2004 to 2011	82 of 101 (81%) patients	Retrospective 36 months	ILFT: Lung volumes, forced flows and tidal mechanics	In those with CDH and PH had significantly higher FRC, FRC/TLC and RV/TLC
Cauley, 2015(27) 201 CDH, born 1995 to 2001	83% at one year and 70% at five years	Retrospective review of 201 medical records 5 years	Adjusting for defect, size and presence of VP mismatch greater pulmonary support at 30 days was associated with developmental delay at one year and asthma and developmental referral at five years	Supplementary oxygen and developmental referral at one year Asthma and developmental referral at 5 years
Rygl, 2015(28) 30 CDH, born – not	Not clear	Prospective 1.32 years	ILFT: Tidal breathing parameters, whole	High incidence of peripheral airway obstruction

Supplementary Table S1: Pulmonary morbidity

clear			body plethysmography, rapid thoraco-abdominal comparison	
King, 2016(29) 41 CDH, born 2002 to 2010	41 or 43 (95%) patients	6.5 years	Association of O/E LHR with growth, neurodevelopmental outcomes, V/Q scans	Similar outcomes at follow up
Benoist, 2016(30) 92 CDH, born 2009 to 2013	86 of 92 (93%) patients	Prospective Discharge to 24 mos	Rate of hospitalisation for wheezing	56% had wheezing episodes
Bojanic, 2016(31) CDH born 1990 to 2010	27 of 38 (71%) patients	Cross-sectional prospective case-control study 7 (5-20) years	CPET, spirometry	Compared to controls CDH survivors had lower anaerobic exercise capacity
Spoel, 2016(32) 9 CDH (1 ECMO-CDH), non-smoking, born 1975 to 1993	Not clear	Cross-sectional 28.4 years (18.1-30.6 years)	Hyperpolarised ^{3}HeMR and anatomical ^{1}HMRI	Functional and microstructural changes persist into adulthood
Ost, 2016(33) CDH born 1990 to 2009	75%	Prospective questionnaire Up to 18 years, range not given	Self-reported health and physical status	Greater problems with asthma
Haliburton, 2017(34) 33 CDH, born 1996 to 2010	33 of 118 (28%) patients	Routine FU 5-17 years	Body mass index, resting energy expenditure and pulmonary function	Mean Z-scores for FEV_1 and FEV_1/FVC were below normal Correlation between BMI and lung function

Supplementary Table S1: Pulmonary morbidity

ABBREVIATIONS

1HMRI	1H magnetic resonance imaging
3HeMR	3He magnetic resonance
AWD	Abdominal wall defect
BMI	Body mass index
BPD	Bronchopulmonary dysplasia
CDH	Congenital diaphragmatic hernia
CPET	Cardiopulmonary exercise testing
CXR	Chest radiograph
CRS	Compliance of the respiratory system
DLCO	Transfer factor for carbon dioxide
ECG	Echocardiography
ECMO	Extra corporeal membrane oxygenation
FEF_{25-75}	Mean forced expiratory flow between 25% and 75% of the FVC
FeNO	Exhaled nitric oxide
FETO	Fetoscopic tracheal occlusion
FEV_1	Forced expiratory volume at one minute
FRC	Functional residual capacity
FRCpleth	Functional residual capacity (by plethysmograph)
FVC	Forced vital capacity
GORD	Gastro-oesophageal reflux disease
ILFT	Infant lung function testing
LCI	Lung clearance index
LHR	Lung head ratio
MMV	Maximum voluntary ventilation
PCA	Post-conceptional age
RRS	Resistance of the respiratory system
RCT	Randomised controlled trial
RSV	Respiratory syncytial virus
RV	Residual volume

Supplementary Table S1: Pulmonary morbidity

SPECT	Single photon emission computed tomography
TLC	Total lung capacity
Tptef/tE	Time to peak expiratory flow/expiratory time ratio
Vmax	Maximum flow
VQ	Ventilation perfusion

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Supplementary Table S1: Pulmonary morbidity

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Supplementary Table S1: Pulmonary morbidity

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Supplementary Table S2: Morbidity of pulmonary hypertension

Reference (population)	Proportion available at FU	Time frame of FU	Outcome description
Catheter studies			
Zussman, 2012(1) 8 repaired CDH, 10 age-matched controls (PDA closure), born 2007-2010	8/8 (100%)	Retrospective case-control study. 8 CDH age 16.9 +/- 9.3 months. 10 controls age 17.3 +/- 8 months.	Baseline echocardiographic assessment of PAP using TR and PDA flow. Cardiac catheter measurement of PAP and PVR. Echo findings in CDH group: 3/8 (38%) PAP> 40% systemic BP. Catheter data: Mean PAP and PVR significantly higher and pulmonary blood flow lower in CDH group. PAP CDH group 23 ± 3 mmHg, Control group 18 ± 4 mmHg. Echo and catheter findings of PH associated with poor growth and respiratory symptoms.
Kinsella, 2005(2) 7 CDH patients with prolonged PH referred to PH clinic Year of birth not stated.	7/7 (100%)	Age at cardiac catheterization: 4 years (3 months -12 years) Median follow-up after catheterization: 12 (6-36) months	Cardiac catheter assessment of PAP: median(range) 60 (23-66) mmHg Additional findings: left PA stenosis/hypoplasia 3/7 (43%), pulmonary vein stenosis/delayed return in ipsilateral lung 6/7,86%; contralateral lung 2/7 (29%). Follow-up: Two deaths from PH at ages 8 years and 19 months. Therapies: O_2 n=7, iNO n=2, prostacyclin n=2, bosentan n=1.
Echo studies			
Trachsel 2006(3) 23 CDH and 23 gender/age matched controls Year of birth not stated.	20/23 (87%) CDH	Cross-sectional, mean age 13.2+/- 2.2 years (10-16) years.	Echocardiographic assessment of PAP and cardiac function. Pulmonary function and exercise testing. Echo data for 20 CDH subjects: Mean resting RV Resting RV systolic pressures 27±6 mmHg : 26-30 mmHg in 4 patients, 31-37 in 3 patients. Mean LV ejection fraction 70±7 %. Mean ipsilateral PA diameter significantly smaller than contralateral side, but within normal range.

Supplementary Table S2: Morbidity of pulmonary hypertension

			Exercise capacity mildly reduced in CDH compared to controls.
Stefanutti, 2004(4) 24 children with mild/moderate CDH. Year of birth not stated.	24/24 (100%)	Retrospective case study. Mean age 8.15 +/- 2.8 years	Echocardiographic assessment of PAP using TR estimate of RVSP and pulmonary perfusion scanning. Echocardiography: RVSP 24.43±3.57 (range 20-30) mmHg. Mean LV ejection fraction 68±6 (range 56-68)%, "within normal range for age". Additional echo findings: moderate TR (n=1), aortic regurgitation (n=1) and hypoplastic left PA (n=1). Perfusion scans: Mean perfusion to affected side significantly lower.
Kamata, 2005(5) 56 infants with high-risk CDH; born 1986-2000	33/56 (59%)	Case study, mean age 11.4 +/- 4.8 years.	Echocardiographic assessment, ventilation and perfusion scintigraphy, growth assessment. "two infants underwent repair of VSD and aortic regurgitation…the others had a normal echocardiographic study". No other echo data reported.
Dillon, 2004(6) 57 CDH; single centre; born 1991-2002	47/57 (82%)	Retrospective chart review; early outcome (60 days)	Echocardiographic estimation of PAP using TR, expressed as ratio of PAP:SBP: PAP<0.5: 23/47 (49%); PAP 0.5-1:16/47 (34%); PAP>1: 8/47 (17%) All infants with PAP:SBP>1 at 3 weeks died at 6 weeks.
Lusk, 2015(7) 140 CDH (27 died); born 2002-2012	140/140 (100%)	Retrospective chart review, early outcome (until discharge)	Echocardiographic assessment of PH using hierarchy of PDA flow, septal position, TR. PH severity classification: "No PH", PAP<2/3 SBP; "moderate PH", PAP=2/3 to SBP; "severe PH", PAP≥SBP . PH resolution before death or discharge in 98/140 (70%). Time to PH resolution (<2/3 systemic) of PH was 14 (7-21) days. 15/140 (11%) discharged with at least moderate PH.
Kipfmueller, 2017(8) 26 CDH treated with IV sildenafil at single institution	26/26 (100%) (Data only on CDH patients	Retrospective chart review. Assessment of PH at baseline (first 24 hours), 14 days, 30 days and discharge.	Echocardiographic assessment of PH using methods and classification as per Lusk 2015. Baseline (first 24 hours): moderate PH in 10/26 (38.5%), severe PH in 15/26 (61.5%) infants. 14 days: No PH or mild PH in 75%

Supplementary Table S2: Morbidity of pulmonary hypertension

	meeting criteria for IV sildenafil therapy.)		30 days: No PH mild PH in 86% Discharge (median 99, range 27-394 days): No PH 84%, mild PH 10%, moderate PH 3%.
Kraemer, 2017(9) 52 CDH born 2010-2014	52/78 (67%)	Prospective follow-up at 6 and 12 months	Echocardiographic and electrocardiographic assessment of PH. Four patients had persistent PH at follow-up.
Other echo measures			
Egan, 2012(10) 7 CDH, 16 controls	7/7 (100%)	Prospective case-control study in 7 CDH (6±2 years) and 16 controls (6±2 years).	Echocardiographic assessment of PAP (TR, septal position), RV dimensions and RV function (myocardial velocities, and global strain). No evidence of PH defined as flattened septum or TR>2.5 RV and LV function qualitatively normal. RV early diastolic and systolic velocities significantly lower in CDH group. Non-significant trend of lower global RV strain in CDH group No significant differences in RV dimensions or area change.
Sildenafil use			
Hunter, 2009(11) 80 CDH; born 2000-2006	80/80 (100%)	Retrospective case series, 80 CDH patients. Age 0-6 years at follow-up.	Oral sildenafil use: 22 (28%) of CDH patients received oral sildenafil. Sildenafil use increased from 0 to 5 (45%) between 2000-2009.
Behrsin, 2013(12) 122 CDH; single centre; born 2005-2012	122/122 (100%)	Retrospective case series. Age 0-7 years at follow-up.	Oral sildenafil use at discharge and follow-up. 19/122 (17%) CDH survivors discharged on oral sildenafil. Duration of sildenafil after discharge median (range) 343 (105-671) days.

Abbreviations: CDH, congenital diaphragmatic hernia; TR, tricuspid regurgitation; PDA, patent ductus ateriosus; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; PA, pulmonary artery; SVR, systemic vascular resistance; PH, pulmonary hypertension, iNO, inhaled nitric oxide; RVSP, right ventricular systolic pressure;

Supplementary Table S2: Morbidity of pulmonary hypertension

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Supplementary Table S3: Neurodevelopmental morbidity

Reference (population)	Proportion available at FU	Time frame of FU	Method of outcome evaluation	Outcome description
Jakobson, 2009(1) 56 CDH 10-16 years, non-ECMO (results of same cohort described in Frisk 2011)	15/56 (27%)	Cross-sectional, 10-15.9 yrs (2 not in analysis due to global delay)	11 controls; 13 CDH WISC (IQ); visual and fine motor domains (6 subtests WISC; 6 additional standardized tests); US and Canadian references	2/15 IQ <50 (not tested). Normal overall intelligence. Visual motor integration and oral-motor programming mildly, but sign lower than controls
Peetsold, 2009(2) 33 high-risk CDH; non ECMO, born 1987-1999	33/40 (83%)	Cross-sectional, 6-16 yrs (mean (SD) 10.2 (3.3) yrs)	WISC-R; Beery VMI; Bourdon Vos (dot cancellation test); CBCL; TRF; CHQ; HUI (all Dutch references)	IQ 100 +/- 13; VMI normal, sustained attention impaired. CBCL: 21% clinical problems; TRF 13% clinical problems
Nijhuis, 2009(3) 32 ECMO-CDH, nationwide, born 1998-2000	4/36 (89%)	Prospective 5 yrs	RAKIT IQ; M-ABC; CBCL (all Dutch references)	Motor function normal in 47%; average IQ normal; behavior not different from norm
Gischler, 2009(4) 12 ECMO/non-ECMO unknown, born 1999-2001,	unknown	Prospective, longitudinal 6-12-18-24 mos	BOS 2-30 (Dutch references)	Mean mental development normal over time (90.1-99.4); mean psychomotor development stable over time (82.6-86.1; mild delay)
Van der Cammen, 2010(5) CDH-ECMO (54%), non-ECMO (46%), born 1999-2003	24/37 (65%)	Prospective 5 years	M-ABC (Dutch references)	58.3% normal motor function (ECMO/non-ECMO not analysed separately)
Danzer, 2010(6) 52 CDH (ECMO 27%; non-ECMO 73%), born 2004-2007	41/52 (79%)	Prospective, < 4 yrs (n=36); >4 yrs (n=5); mean (range) 25.4 (6-62) mos	BSID-II (< 2006); BSID-III (> 2006); WPPSI > 4 yr (all US references)	BSID-cognition/ language;average, mixed, mildly delayed, and severely delayed in 49%, 19%, 17%, and 15%, resp. Psychomotor scores were normal, mildly delayed, and severely delayed in 46%, 23%, and 31%. 31% normal on all domains; 16% significanty delayed on all domains. WIPPSI below expected. ECMO sign predictor poor outcome
Frisk, 2011(7) (see Jakobson 2009)				

Supplementary Table S3: Neurodevelopmental morbidity

Tureczek, 2012(8) CDH-nonECMO, born 1994-2005; without genetic syndrome 26/33, with genetic syndrome 7/33	33/39 (85%)	Cross-sectional, median 7.9 years (range 3.3-14.8 years)	WPPSI-III (3-6 yrs), WISC-IV (> 6 yrs) (German versions, reference?), M-ABC-2 (3-5 yrs) (reference?), Zurich Neuromotor Assessment (>5 yrs) (reference?).	Without genetic syndrome: Cognition normal (median (range) 103 (75-121)); >5 yrs significantly lower scores on adaptive fine and gross motor score (80% abnormal gross motor function). Genetic comorbidity only predictive factor.
Danzer, 2013(9) CDH-ECMO (26%) and non ECMO (74%), n=80, born 2004-2010	47/80 (59%) at least twice	Longitudinal, first median (range) 8 (5-15) mos, last median (range) 29 mos (23-36) mos	BSID (II < 2006; III > 2006 (US references)	Neurocogn and language: initial: 70% average-low average; 30% mild-severe delay; last: 76 vs 24%, resp. Motor: initial: 55% average-low average; 45% mild-severe delay; last: 81 vs 19%, resp.
Danzer, 2013(10) CDH-ECMO (23%) and non-ECMO (77%), born 2006-?, n=60	60/60 eligible (> 2yrs)	Prospective 28 ± 4.5 mos and 58 ± 4.0 mos; most recent evaluation in analysis	BSID-III (n=42) and WPPSI-III and Beery VMI (n=18); (US references)	BSID-III: 36% mild to severe deficits in at least one domain; 7% patients demonstrated severe delays for all scales. Mean (SD) scores for cognition, language, motor: 90.7 (14.3); 96.7 (19.1); 92.1 (15.7) WPPSI-III: 103.6 (8.4); VMI 89.2 (10.2). ECMO and other severity disease assoc low scores
Wynn, 2013(11) CDH-ECMO (14%) and non-ECMO (86%), born 2007-2010 multicenter DHREAMS, n=53	49/53 (92%)	Prospective 2 years (mean 24.6 +/- 1.3 mos)	BSID-III, VABS-II (US references)	BSID-III: Cogn: 93 +/- 15; language: 95 +/- 16; motor: 95 +/-11 (all sign below norm) VABS: sign lower scores mean daily living, social skills, motor skills. Need for ECMO associated dev delay (but only 14%!)
Benjamin, 2013(12) High-risk CDH non-ECMO (75%) and ECMO (25%), born 2001-2005	16/24 (67%)	Cross-sectional > 4 years (4.3 to 7.5 yrs)	WPPSI-III, TELD-3 (language); US references. NCD (neurocogn. delay if any score < 80)	Overall FIQ 89; 44% NCD (median FIQ 81); 56% no NCD (median FIQ 99). Expressive language < 80 in 33%.
Madderom, 2013(13) n=35, single center, born 1999-2003	35/41 (85%)	Prospective 8 years; CDH-ECMO (n=16); non-ECMO (n=19)	RAKIT/WISC; Bourdon-Vos (dot cancellation test); M-ABC (all tests Dutch references)	Mean (SD) IQ ECMO 91.7 (19.5); non-ECMO 111.6 (20.9). Problems with concentration (68%) and with behavioural attention (33%); motor function delay in 16% (all irrespective groups)
Madderom, 2013(14)	?; overall ECMO	Prospective 8 years	RAKIT/WISC; Beery VMI;	Mean (SD) IQ 96.6 (18.6); mean (SD) VMI 91.0

Supplementary Table S3: Neurodevelopmental morbidity

30 ECMO-CDH, nationwide, born 1996-2001	141/179 (79%)		Bourdon-Vos (dot cancellation test); (all tests Dutch references)	(16.4); Bourdon-Vos 30% slow-very slow working speed.
Michel, 2013(15) 31 non-ECMO; 1 ECMO, multicenter, born 1999-2008	32/52 (62%)	Cross-sectional 6.7 +/- 3.3 yrs	Questionnaires: Kidscreen27; SDQ; parents: SF-36 (French references)	Both QoL scores of children and parents significantly below the norm
Leeuwen, 2014(16) CDH-non ECMO, born 2006-2009	18/29 (62%)	Longitudinal 1 (n=18) and 3 years (n=15)	BSID-III; matched controls and US references	Compared to controls normal development; compared to reference: At 1 yr 18% severe motor delay motor, normal at 3 yrs. At 1 and 3 yrs 6 and 21% mild delay expressive language
Van der Cammen, 2014(17) 49 ECMO-CDH, nationwide	? (overall ECMO 254/318 (80%))	Prospective, longitudinal at 5, 8, 12 yrs	M-ABC (Dutch references)	Mean (95%-CI) Z-score M-ABC at 5, 8, 12 yrs: -0.73 (-0.44 to -1,03), -0.33 (-0.02 to -0.65), -1.48 (0.87 to -2.09)
Bevilacqua, 2014(18) CDH 2008-2010 (see Bevilacqua, 2015)				
Kubota, 2015(19) CDH (unknown ECMO or not), n=21, born 1992-2003 (n=53 survivors)	n=21 (randomly invited) from 53 survivors	Cross-sectional, 6-17 yrs	WISC; CBCL; QoL: Kid-KIND Also evaluation (PTSD) of mothers. No information on references.	Mean (SD) IQ 80.9 (33.7); T-score CBCL mean (SD) 55.3 (10.8); QoL?? (not mentioned)
Bevilacqua, 2015(20) High-risk CDH-non ECMO, > 33 w gestation, born 2008-2012	42/46 (87.5%)	Prospective, longitudinal 6 and 12 mos	BSID-III (Italian, US references)	Mean (SD) mental 92.2 (15.1) and 96.5 (13.7) at 6 and 12 mos; mean (SD) motor 92.2 (16.9) and 92.9 (17.2)
Danzer, 2015(21) Non-ECMO CDH, born 2005-2012 (overlap with previous studies?!)	63 consecutive; missing data?	Prospective, 12 mos (10-14 mos)	BSID-III (US references)	All scores below normal, mean (SD) mental 93.7 (14.4), motor 89.6 (14.6), language composite 85.9 (13.8). 43% average all scales, 44% mild delay, 13% severe delay in at least one domain. Risk: illness severity, feeding problems
Snoek, 2016(22) High-risk CDH, multicentre, non-ECMO (93%), ECMO	81/98 (83%)	Prospective, longitudinal 12 and 24 mos; Rome n=39 non-	BSID-II-NL (Dutch) and BSID-III (Italian, US references)	Rome: 12 and 24 mos: cognition: mean (SD) 97.9 (11.8) and 102.1 (13.9); motor: mean (SD) 93.2 (12.2) and 98.2 (14.8).

Supplementary Table S3: Neurodevelopmental morbidity

(7%), born 2009-2012		ECMO; Rotterdam n=36 non-ECMO; n=6 ECMO (12% of Dutch cohort)		Rotterdam: 12 and 24 mos: cognition: mean (SD) 97.8 (19.8) and 96.0 (18.4); motor: 87.7 (18.8) and 82.9 (16.7).
Toussaint, 2016(23) 26 ECMO-CDH, nationwide, born 1996-2004 (overlap with patients in Van der Cammen, 2014(17))	?; overall ECMO 177/251 (71%)	Prospective 8 yrs	M-ABC; SPPC; PedsQL (all tests Dutch references)	Normal motor function in 16/26 (62%); normal scores self-esteem and perceived motor competence; impaired health status (z-score total score mean (SD) -1.43 (1.29))
Leeuwen, 2017(24) 10 ECMO-CDH and 30 non-ECMO CDH; single centre; born 2006-2009 (25 ECMO-non CDH)	18/83 (78%) overall group	Prospective 8 yrs	WISC-III-NL; extensive neuropsychological tests (all Dutch references)	Mean (SD) IQ 84 (12) and 100 (20) in ECMO-CDH and non-ECMO CDH, respectively. Sustained attention, verbal and visuospatial memory deficits in whole group. Maximal vasoactive inotropic score within first days was negatively associated with verbal and visuospatial memory

CDH: congenital diaphragmatic hernia; ECMO: Extracorporeal Membrane Oxygenation; IQ: intelligence quotient; VMI: visuomotor integration; NCD: neurocognitive delay

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Supplementary Table S3: Neurodevelopmental morbidity

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Supplementary Table S3: Neurodevelopmental morbidity

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Supplementary Table S4: Morbidity of sensorineural hearing loss

Reference (population)	Proportion available at FU	Time frame of FU	Method of outcome evaluation	Threshold	Outcome (SNHL)	Risk factors/notes
Amoils, 2015(1) CDH patients with at least 1 audiological FU; born 1999-2008	50 (% unknown)	Mean (range) 2.7 (0.5-10.7) yrs	Pure-tone audiogram (behavioural)	20 dB 40 dB	28/50 (56%) 9/50 (18%)	ECMO; L-MV; patch; dose furosemide Newborn screening normal in 40/47 (85%) tested
Dennett, 2014(2) Repaired CDH diagnosed < 12 mos age with at least 1 audiogram; born 2000-2011	122/151 (80%)	?	Newborn/young infants: ABR/Evoked Potentials Older: frequency-specific behavioural	20 dB	9/122 (7%)	L-MV, L-NICU, LOS, L-aminoglycosides Multivariate: L-aminoglycosides
Partridge, 2014(3) CDH survivors enrolled in pulm. hypl program; born 2004-2012	112/225 (50%)	? In theory FU up to 3 yrs.	Newborns: TEOAE, ABR Outpatients: behavioural, OAE, ABR	20 dB in 2 freq.	SNHL: 3/112 (3%) CHL: 38/112 (34%) HL NOD 5/112 (4.5%)	ECMO, L-OS, L-MV, L-diuretics, L-aminoglycosides, APGAR 5' High prevalence of conductive HL. All SNHL diagnosed before NICU discharge.
Wilson, 2013(4) High-risk CDH survivors; born 2000-2010	42/44 (96%)	? In theory FU up to 3 yrs.	AABR/ABR; age-appropriate audiogram; impedance; OAE	?	1/42 (3%)	1 more pt with mild unilateral deficit Pt with SNHL had normal screening before discharge
Van den Hondel, 2013(5) ECMO-treated CDH survivors; born 1992-2005	24 (% unknown)	? In theory 6-12-24 mos 5-8-12 yrs	Audiometry Tympanometry	20 dB	2/24 (8%)	No difference between CDH and other diagnosis
Safavi, 2012(6) CDH survivors 2 centres; born 2005-2007	44/44 (100%)	? Up to 10 yrs	?	?	5/44 (11%)	Multicenter study with different FU programs
Morando, 2010(7) High-risk CDH survivors; born 2003-2009	26/32 (81%)	Median (IQR) 2 (1-4.5)	Newborns: A-TEOAE/A-ABR Older: behavioural; OAE; tympanometry; acoustic reflex	20 dB in 2 freq.	1/26 (4%) CHL: 4/26 (16%)	Patients with SNHL had normal newborn screening. 4 patients had only newborn screening
Javidnia, 2009(8)	17/19	?	?	?	6/17 (35%)	Normal neonatal screening in 5

Supplementary Table S4: Morbidity of sensorineural hearing loss

CDH survivors; born 1998-2006	(90%)					L-NICU, L-MV
Morini, 2008(9) High-risk CDH-non ECMO; born 1999-2005	82/87 (94%)	Median (IQR) 3 (1.4-4.5) yrs	< 12 mos: OAE or AABR Older: repeated behavioural audiometry	20 dB	40/82 (49%)	Univariable: GA, L-MV, L-aminoglycosides, L-pancuronium, L-diuretics, iNO, age at test, N. sepsis, N. hypocapnia Multivariable: age at test
Masumoto, 2007(10) High-risk CDH survivors; born 1997-2005	16/18 (89%)	Range 1-8 yrs	<12 mos: A-ABR Older: A-ABR; behavioral	30 dB	4/16 (25%)	Normal neonatal screening in all L-MV, L-HFOV, L-diuretics, L-pancuronium, Dose pancuronium
Fligor, 2005(11) CDH surivors treated ECMO; born 1986-1994	22 (% unknown)	? Up to 42 mos	ABR; behavioural	20 dB or 30 dB depending on freq. and test	13/22 (59%)	CDH independent risk factor in ECMO graduates. L-ECMO; L-aminoglycosides
Cortes, 2005(12) Severe L-CDH survivors (LHR<1.4); born 1999-2001	16 (% unknown)	36 mos	Newborn: A-ABR Older: Clinical, if concern >> behavioural	?	8/16 (50%) (7 require amplification)	Normal neonatal screening in 6. Progressive increase of prevalence with ageing.
Robertson, 2002(13) Severe CDH survivors (2 OI>25 15 min apart; born 1994-1996	15/15 (100%)	48 mos	Newborn: ABR; TEOAE/DPOAE Post-discharge: tympanometry; developmental-appropriate behavioural; ABR, TEOAE	18-24 mos: 40 dB 4 yrs: 25 dB	15/15 (100%)	No difference between ECMO-treated and non-ECMO-treated patients
Jaillard, 2002(14) CDH survivors; born 1990-1998	51/51 (100%)	24 mos	Boel test; brainstem auditory-evoked potential	?	0/51 (0%)	
Rasheed, 2001(15) CDH survivors ECMO graduate; born 1984-1994	15/21 (71%)	Mean (range) 7,4 (3-9) yrs	Tympanometry, behavioural	30 dB or need for ampl.	8/15 (53%)	L-ECMO, L-furosemide, L-alkalosis

Supplementary Table S4: Morbidity of sensorineural hearing loss

Abbreviations: ABR: auditory braistem response; A-ABR: automated ABR; CDH: congenital diaphragmatic hernia; CHL: conductive hearing loss; ECMO: extracorporeal membrane oxygenation; FU: follow-up; GA: gestational age; HFOV: high frequency oscillatory ventilation; L: length; LOS: length of stay; MV: mechanical ventilation; NICU: neonatal intensive care unit; NOD: not otherwise defined: OAE: otoacoustic emissions; SNHL: sensorineural hearing loss: TEOAE: transient evoked OAE

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Supplementary Table S4: Morbidity of sensorineural hearing loss

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Supplementary Table S5: Gastrointestinal morbidity and growth

Gastroesophageal Reflux					
Reference (population)	**Proportion available at FU**	**Time frame of FU**	**Method of outcome evaluation**	**Outcome description**	**Comments**
Arena, 2008(1) CDH from two eras Group A 1997-2002 (n=12) Group B 1972-1996 (n=19)	31/38 (82%)	Cross-sectional, Group A mean 4.5 ± 1.8 yrs (range 2-7 yrs); Group B mean 21 ± 5.7 yrs (range 8-33 yrs)	Physical examination, barium meal study, GE scintigraphy, pH monitoring, manometry esophagus and stomach, endoscopy if GER	Group A: 41.7% GER symptoms 33.3% barium meal pathology 58% GER on scintigraphy 41.7% delayed stomach emptying 54.5% GER on pH metry 36.4% altered peristalsis Group B; 15.8% GER symptoms 21 % barium meal pathology 42% GER on scintigraphy 47% delayed stomach emptying 33.3% GER on pH metry 46.7% altered peristalsis Total: 33% GER on endoscopy	
Muratore, 2001(2) 121 CDH (100 left, 21 right); birth years not stated	?	Longitudinal Children tested 1990 to 2000 in multidisciplinary clinic	Upper gastro intestinal tract examination in FTT and GERD symptom patients FTT defined as average daily	56% FTT in year 1 25% oral aversion	-Related to ECMO need and patch repair, oral aversion -Related to

Supplementary Table S5: Gastrointestinal morbidity and growth

		Testing at 6, 12, 24 and 36 mos (percentage of patients available at FU not reported)	weight gain less than expected for age and sex, negative crossing of weight and height percentiles, or persistent weight for height < p5	33% FTT+ gastrostomy need 45 UGI series showed 60% GERD and 21 of the total group had fundoplication	duration of ventilation and need for oxygen at discharge -Related to duration art ventil and patch repair All patients treated with H2-blockers
Peetsold, 2010(3) 69 non-ECMO CDH; born 1987-1999	69/131 (53%) at 2 yrs 58/131 (44%) at 6 yrs	Cross-sectional 2 yrs (early), 6 yrs (late)	Standardized score. If score > 3 additional investigations. Early GERD: UGI series and/or endoscopy and or 24 h pH metry Late GERD: reflux questionnaire	Early GERD 39% Late GERD suspected in n=9. Confirmed in 12%	-Related to patch closure and stomach position -No risk factors identified
Koziariewicz, 2014(4) 50 CDH, born ?	?	Cross-sectional 3 mos-18 yrs	pH metry (n=48) UGI contrast series (n=5) Physical growth	Signs of GERD: 15/59 (30%) Confirmed by pH metry in 13/48 (27%) Growth:20% < p3	-GERD suggested by spitting, vomiting recurrent bronchitis and pneumonia - Related with patch use, prolonged ventilation and HFOV
Terui, 2014(5) 182 CDH; born 2006-2010; nationwide	182/182?	Retrospective; longitudinal? Up to six years?	Medical record evaluation: incidence of GERD and surgery	23.8 % medication for GERD 10.7% reflux surgery	-Related with antenatal diagnosis and tube feeding at discharge -Related to

Supplementary Table S5: Gastrointestinal morbidity and growth

					gestational age and defect size
Yokota, 2014(6) 74 CDH; born 1997-2013	?	Cross-sectional, retrospective Median 50 (5-225) mos	Medical record evaluation: GERD surgery	GERD 37.8%	Related to stomach herniation
Maier, 2011(7) 79 left-sided CDH randomized to primary antireflux surgery or not during CDH repair; patient-blinded; born 2003-2009 43 without antireflux surgery; 36 with antireflux surgery	6 mos: 63/79 (79.7%) 12 mos: 58/79 (73.4%) 24 mos: 53/79 (67.1%)	FU at 6-12- 24 mos	Questionnaire on GERD symptoms at FU. Classification of GERD severity based on symptoms (5 degrees). Upper GI and pH metry in patients with severe GERD symptoms or failure to thrive Failure of antireflux surgery defined as need for fundoplication, gastrostomy or jejunostomy	GERD at 6 month: 10/28 (35.7%) with antireflux surgery and 21/35 (60%) in control (p=0.055) GERD at 24 month: 5/24 (20.8%) with antireflux surgery and 6/29 (20.7%) in control (p=0.99) 8/36 (22.2%) in intervention group presented failure of antireflux surgery. In control group 3/43 (7%) with need for fundoplication, gastrostomy or jejunostomy. No difference in failure to thrive	Advise: no primary anti reflux surgery.
Morandi, 2015(8) 12 CDH undergoing general anesthesia for surgery between Jan and Oct 2013	all	Mean age 14.5 yrs (9-18 yrs)	GERD Esophagitis severity	Questionnaire: n=3 (25%) pathological score Endoscopy: n=3 (25%) grade 1 esophagitis; n=6 (50%)	

Supplementary Table S5: Gastrointestinal morbidity and growth

				grade 2; n=2 (17%) grade 3; n=1 (8%) grade 4; n=1 had Barrett esophagus	
Caruso, 2013(9) 36 CDH	?	Longitudinal? 6 mos and 5 yrs	pH-Multichannel intraluminal impedance (MII) at 6 median months pH-MII and endoscopy at median 5 years	At 6 months: 62% symptoms At 5 years 38% symptoms At 6 months 83% GERD At 5 years 61% GERD High incidence of reflux and esophagitis also in asymptomatic pts	Risk factors for reflux: patch, intrathoracic stomach, esophageal dysmotility. Mainly non-acidic reflux
Verbelen, 2013(10) 62 CDH; born 1993-2009	62/69 (90%)	Retrospective chart review Median 4.0 yrs (0.2-14.9)	Clinical symptoms of GERD, confirmed by UGI.	GERD 31/62 (50%); antireflux surgery 13/62 (21%) at median 64 (37-264) days	Liver herniation was only independent predictor for GERD and surgery
Di Pace, 2011(11) 30 CDH; born 2002-2007	?	Cross-sectional Median 5.2 years (3-10 years)	pH multichannel intraluminal impedance	86% GERD mainly non acidic, postprandial, short term, distal esophagus; dismotility only distal.	
Kawahara, 2010(12) 66 CDH; born 1996 to 2007	52/66 (78.8%)	Median 108 mos (range 31-167)	24 hr pH-metry for reflux index: % time with pH < 4.0;	Reflux index: 0.1-44.3% Reflux index > 10% (pathological) in 22/52 (42.3%)	Reflux symptoms ameliorated at age 3 years
Koivusalo, 2008(13) 26 CDH, born 1990-2006	26/26?	6 mos, 1, 3, 5 and 10 yrs	Symptoms evaluation all assessments; endoscopy and pH-metry at 1 year; endoscopy and pH-metry for patients with symptoms and complications of GERD at 3-10 years. GERD: need for surgery, moderate or more	Significant GERD: 6 mos 7 of 26 (27%) 1 yr 11 of 26 (42%) 3 yrs 8 of 15 (53%) 5 yrs 8 of 15 (53%) 10 yrs 5 of 9 (55%)	In patients that required anti reflux surgery this was manifest before 6 mos.

Supplementary Table S5: Gastrointestinal morbidity and growth

			esophagitis on endoscopy, total reflux index > 10% or postprandial reflux index > 5% on pH-metry		
Diamond, 2007(14) 86 CDH, born 1995-2002	?	Retrospective; 3-10 yrs	Determine children with GERD intervention (fundoplication or gastro intestinal tube) Study predicting factors for intervention.	Descriptive GERD incidence and related factors	
Kamiyama, 2002(15) 26 CDH	?	Mean 1.7 +/- 0.9 mos	pH-metry: RI= reflux index = % total time pH < 4.0	Group A: RI < 4.0 % (n=7) Group B; RI > 4.0% Group A more primary closure diaphragm; group B more intrathoracic liver	
Öst, 2016(16) 109 CDH, born 1990-2009	109/145 (75%)	Cross-sectional, self assessed physical health at 2010	Questionnaire including antropometrics. 4 groups: 1: not intubated with 6 hrs; 2: intubated < 6 hrs, no ecmo 3; ecmo 3b; 2nd ecmo run	GI symptoms: Group 1: 15%, Group 2: 49%, Group 3: 71%, Group 3b: 57% Eating taking more time Group 1: 5%, Group 2: 27%, Group 3: 50% GER symptoms: Group 1: 3%, Group 2: 22%, Group 3: 25% Abdominal pain: Group 1: 13%, Group 2: 33%, Group 3: 21% Growth:	

Supplementary Table S5: Gastrointestinal morbidity and growth

				Group 1: all within -2sd, Group 2: 18% < -2sd, Group 3: 35% < -2sd	
Zanini, 2017(17) 21 CDH survivors, born 2014-2015; 76% A or B type defect	21/21 (100%)	Prospective 1 yr	Routine 24h pH metry, questionnaire on symptoms	4/21 (19%) symptomatic GER 1/21 (5%) RI > 10%	Patch repair and ECMO predictors of GERD and fundoplication
Su, 2007(18) 39 CDH, born 1997-2005	39/42 (93%)	Retrospective During initial postnatal hospital stay	Chart review for symptoms of GERD and fundoplication	GERD: n=21 (54%) Fundoplication: n=9 (23%)	Patch repair and ECMO predictors of GERD and fundoplication
Failure to thrive and GERD					
Jailard, 2003(19) 51 CDH, born 1991-1999	51/85 (60%)	Follow up at 2 yrs	Recording early (<2 months) and late >2 months) mortality. Respiratory, nutritional, musculoskeletal, neurosensory outcome at 2 years follow up Growth retardation <p5 GERD assessed by pH monitoring Oral dysfunction defined as sucking-swallowing reflex anomalies with oral aversion	Growth failure in 9/51 (18%), related to GERD and oral aversion Symptomatic GERD in 14/51 (27%) Oral dysfunction in 13/51 (25%)	
Crankson, 2006(20) 45 CDH, born 1993-2002	31/45 (68.9%)	Retrospective 6 mos to 9 yrs – only data from last documented FU visit	Medical record review for growth and GER Failure to thrive: growth <p5	GER 8/31 (26%) FTT: 7/31 (23%)	

Supplementary Table S5: Gastrointestinal morbidity and growth

Chamond, 2008(21) 36 CDH (Group A: 17 primary fundoplication, Group B: 19 no fundoplication), born 1994 to 2004	?	Non-randomized cohort study). Mean 3 yrs follow up (6-132 mos)	GER diagnosed by pH monitoring, UGI, endoscopy Growth retardation <p5	GER group A: 17.6% GER group B: 52.6% Growth retardation: Group A: 3/17 (17.6%) Group B: 1/16 (6.3%)	
Valfre, 2011(22) 70 high-risk CDH, born 2004-2008	61/70 (87%)	Prospective, longitudinal Testing at 6, 12 and 24 mos	Growth GER defined by clinical symptoms and, if required, barium swallow X ray, pH-metry, scintiscan to rule out the need for surgical treatment of GER	GER % 6 mos: patch 87%; no patch 41% 12 mos: patch 79%; no patch 37% 24 mos: patch 70%; no patch 27% Growth: Z-score weight 6 mos: patch -2.9; no patch -1.3 12 mos: patch -1.5; no patch -0.9 24 mos: patch -1.8; no patch -0.7 Z-score BMI 6 mos: patch -2.5; no patch -1.3 12 mos: patch -1.9; no patch -1.2 24 mos: patch -1.8; no patch -0.9 Z-score length 6 mos: patch -0.6; no patch -0.1	

Supplementary Table S5: Gastrointestinal morbidity and growth

				No differences at 12 and 24 mos	
Leeuwen, 2017(23) 172 CDH, 43 ECMO-CDH, 129 non-ECMO CDH, born 1999-2014, late diagnosis and syndromes excluded.	n = 172/179 (96%)	Prospective, longitudial 0.5, 1, 2, 5, 8, and 12 yrs 0.5 yrs: 170/172 1 yrs: 159/172 2 yrs: 133/152 5 yrs: 100/117 8 yrs: 58/64 12 yrs: 27/30	Growth (including correction for target height), pH-metry (n=138), indirect calorimetry (n=11)	Growth: HFA Z-scores declined from 0.5 to 5 yrs and improved significantly in ECMO pts from 8 to 12 years. Significantly lower HFA in ECMO pts, compared to non-ECMO at 2, 5 and 8 yrs. WFH Z-sores declined from 0.5 to 2 years and improved slightly from 2 to 12 yrs. Significantly lower in ECMO pts compared to non-ECMO from 0.5 to 8 yrs. GERD diagnosed by pH-metry at median age 2.9 (IQR 1.7-4.4) mos: 38%; Nissen-fundoplication: n=20 (12%) at median age 0.7 yrs.	
Bojanić, 2017(24) 28 CDH, 22 non-ECMO, 6 ECMO-CDH, born 2001-2015	28/38 (74%)	Retrospective chart review. Non-ECMO: median 5.6 yrs; ECMO: median 5.1 yrs	Definition of and diagnostic approach to FTT and GERD not reported	FTT: n=10 (35.7%) GERD: n=20 (71.4%)	
Rudra, 2016(25) 85 CDH, born 1997-2013	85/123 (69%)	?, initial hospitalization?	Growth velocities in infants with and without G-tube	Infants without gastrostomy tubes had a	

Supplementary Table S5: Gastrointestinal morbidity and growth

				growth velocity of 6.5 g/day (95% CI: 2.5–10.4) more than infants with gastrostomy tubes	
Haliburton, 2016(26) 43 CDH, 2011 to 2014	43/72 (60%)	6, 12 and 24 months	Energy intake (kcal/kg/d) required for weight gain of 25-30 g/d FTT defined as weight Z-score less or equal to -2	FTT at discharge 16.2% at 12 mos 3.6% at 24 mos 4.2% Stunting 13-19%	
Haliburton, 2015(27) 116 CDH, born 1996 to 2009	Unselected CDH consort. N=116/202 (57%) in 376 outpatient visits	Group A: 5-7 yrs, Group B: 7-10 yrs, Group C: 10-15 yrs, Group D: 15-18 yrs	Antropometric measurements reported as Z-scores Indirect calorimetry (measured resting energy expenditure (mREE) : predicted REE)	All weight, height and BMI scores were below zero. No differences between age groups. FTT A: 7 %, B: 17%, C: 19%, D: 19% Feeding tube during infancy 25%; Feeding tube in situ at 7yrs: 15%; mREE:pREE 104% (83-137%); Hypermetabolism (mREE : pREE > 110%): 58%	
Bairdain, 2015(28) 110 CDH, born 2000-2010	?	FU program at least 12 mos	WFA Z-score	Median (IQR) WFA Z-score at discharge; -1.4 (-2.4 to -0.3); at 12 mos; -0.4 (-1.3 to 0.2) % WAZ < -2.0 decreased	

Supplementary Table S5: Gastrointestinal morbidity and growth

				from 26% to 8.5% from discharge to 12 mos	
Leeuwen, 2014(29) 38 CDH (non-ECMO), born 2005-2011	38/45 (84%); 24/45 (53%) seen all three times	FU at 3, 6 and 12 mos	Antropometric measurements at 3, 6 and 12 months; Z-scores FTT defined as Z-score < -2 WFA or WFH	All z scores at 3 timepoints were below zero. FTT 63% in first 6 mos and 21% at 12 mos	
Pierog, 2014(30) 92 CDH, ECMO-CDH and non-ECMO CDH, born 2007-2012	68/92 (73.9%)	Medical chart review at 12 mos for all survivors	Weight and tube feeding need	35 % < p5 for weight 18% tube feedings	
Kamata, 2005(31) 33 CDH, born 1986-2000	?	11.4 +/- 4.8 yrs	FTT: Growth < 5p	FTT n=7 (21%)	
Dariel, 2010(32) 57 CDH with patch-repair, 34 primary fundoplication, 23 without fundoplication, born 1994 to 2005	? 34/57 (59.6%) Survivors: 29/34 (85.3%) with fundoplication; 14/23 (60.9%) without fundoplication	6 mos, 1 yr and > 1 yr Median FU fundoplication group: 5.0 (2-12.5) yrs. Median FU without fundoplication: 4.3 (3.0-7.2) yrs	Growth evaluation Growth retardation (GR)= WFH Z-score and HFA Z-score < -1.5	9/23 controls needed fundoplication later on (mean age 3.25 mos; range 2-8) 6 mos: 4/26 and 3/13 growth failure At 1 yr: 1/26 and 5/13 growth failure 9/29 versus 11/14 with growth retardation at least once during follow-up Over 1 yr: 20/34 and 5/23 *without growth failure* at last measurement.	

Supplementary Table S5: Gastrointestinal morbidity and growth

Cortes, 2005(33) 16 CDH, randomized trial on tracheal occlusion (7 with, and 9 without)	?	1 and 2 yrs	Anthropometry parameters; growth failure (GF) defined as WFA Z-score < - 2	At 1 yr: GF in tracheal occlusion: 86%; GF in controls: 56% At 2 yrs: GF in tracheal occlucion 33%; GF in controls: 22%	
Terui, 2016(34) 174 CDH; born 2006-2010; nationwide	174/228 (76%)	1.5, 3 and 6 yrs	Medical record evaluation: growth. Growth retardation at any of the three follow up time points: WFH or HFA Z-score < -2.0 Stunting: HFA < 90% Wasting: WFH < 80%	Overall growth retardation: 35/174 (22.7%); 1.5 yrs: 19.5%; 3yrs: 14.4%; 6 yrs: 13.5% With increasing age wasting type of growth retardation declined and stunting type predominated.	Low birth weight and home oxygen treatment were risk factors for growth retardation
Najaf, 2013(35) 22 CDH, born 2006-2010	22/26 (85%)	24 mos to 5 yrs	Growth parameters, review of chart records at FU visit	24 mos: weight < p25: n=9 (40%), weight < p3: n=3. GI problems in 12 pts (55%). Gastrostomy feeding: n=4 (18%)	
Gischler. 2009(36) 20 CDH, born 1999-2003, syndromes excluded	20/22 (91%)	Longitudinal 6, 12, 24, and 60 mos	WFA, HFA and BMI Z-scores	Growth below normal at all ages.	

Abbreviations: BMI: body mass index; CDH = congenital diaphragmatic hernia; ECMO: extracorporeal membrane oxygenation; FTT = failure to thrive; FU = follow up; GER = gastro esophageal reflux, GERD = gastro esophageal reflux disease, GF: growth failure; HFA: height for age; HFOV: high frequency oscillation ventilation; mos: month; p = percentile; RI: reflux index, WFA: weight for age; yrs: years

Supplementary Table S5: Gastrointestinal morbidity and growth

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Supplementary Table S5: Gastrointestinal morbidity and growth

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Supplementary Table S5: Gastrointestinal morbidity and growth

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Supplemental Table S6: Surgical morbidity

Reference (population)	Proportion available at FU	Time frame of FU	Method of outcome evaluation	Outcome description
Nagata, 2015(1) 180 CDH; nationwide (questionnaire, incomplete data); born 2006-2010	180/228 (79%) survived at least 3 yrs	2 year follow up	Recurrence rate at 6-12-24 months; multivariate analysis	Recurrence total: 21 (11,7%); primary 5.4%, patch 22.1 %. liver herniations significant predictor (OR 3.96; 95% CI 1.01-16.92).Patch and defect size C+D not significant.
Jancelewicz, 2013(2) 157 CDH; born 2000-2011; single centre	157/187 patients 84%; (27 died, 3 excluded due to lack of follow-up), FU 0.7-12.3 years	Retrospective; based on follow-up protocol: 4wk (post discharge)-4mos-8mos-12mos-18mos-2yrs-3yrs-5yrs-7yrs-10yrs	X-ray for recurrence SBO Laparotomy Chest wall deformities Scoliosis	Recurrence all 15% (MIS 32% versus open 11%, patch 29% vs primary 10%) Median time to recurrence 0.7y (range 0-8.5), primary 0.4 (0-5.1), patch 1.4 (0-8.5) SBO laparotomy primary 6%, patch 12%
St Peter, 2007(3) 121 CDH, born 1994-2004 single centre	67% (81 of 121 survived repair)	Retrospective; FU 2.2-12.9 yrs (mean 8 yrs). Patch (n=24) versus primary (n=57) repair.	Small bowel obstruction Recurrence Fundoplication Subsequent abdominal operation	Patch 21% vs primary 5% Patch 25% vs primary 7% Patch 21% vs primary 11% Patch 63% vs primary 18%
Jancelewicz, 2010(4) 99 CDH; born 2000-2008; single centre different patch material over time period (Goretex or Surgisis until 2006, Goretex and Surgisis after 2006)	98 (99%) survivors, 1 death after discharge	Prospective FU 2000-2008	Recurrence Bowel obstruction and laparotomy	Primary 10% versus patch 46%, hazard ratio patch (versus primary) 5.4 (2-16). Median time to recurrence primary 1.2 yrs, patch 0.9 yrs. 13% total, median 1.2 yrs (range 0.1-3.6 yrs). (54% adhesions, 39% reherniation, 8% volvulus).

Supplemental Table S6: Surgical morbidity

Davis, 2004(5) 27 CDH-ECMO; born 1992-2000	(27/73 /37%) survived	Retrospective	Recurrence Malrotation Other abdominal surgery	11% (3/27) 11% (3/27) 11% (3/27)
Crankson, 2006(6) 31 CDH, born 1993-2002	31/45 newborns (69%), 14 died (31% in total, 24% in neonatal period)	Retrospective; FU 6 mos-9 yrs (no structured FU)	Recurrence SBO Laparotomy for SBO	13% (4/31) 23% (7/31) 10% (3/31)
Tsai et al, 2012(7) 149 corrected CDH; born 1999-2010;	149/184 (81%) (85 (46.2%) primary and 99 (53.8%) patch repair in total) 75 (50.3%) primary and 74 (49.7%) patch repair in survivors)	Retrospective; FU median 18 mos primary, 24 mos patch (no structured FU)	Main: recurrence Secondary: SBO SBO with operation Patch infection	Primary 4%, patch 5.4% Primary 6.7%, patch 5.4% Primary 4%, patch 5.4% Not stated
Cho et al, 2009(8) 57 CDH; born 2001-2004; 29 thoracoscopic, 28 open repair	29/72 thoracoscopic (40%) 28/72 open (39%), 15/72 (21%) died	Retrospective, FU 2wk-1mo-every 3-6mos until 2 yrs (no structured FU)	Recurrence	Thoracoscopic 6/29 (21%) Open 2/28 (7.1%)
Yokota, 2014(9) 83 CDH; born 1995-2013 and 240 newborns with open laparotomy	74/83 (89%) children with CDH, 49 primary and 25 patch repair, 240 controls with abdominal procedures	Retrospective case-control study; FU median 50 mos (4-225)	SBO reoperation Recurrence	17.6% with CDH 6.7% control group 10.8%
Laituri, 2010(10) 155 children with CDH; born 1994-2009 3 types of patch: 37 Surgisis, 12 nonabsorbable (Dacron and Gore-Tex), 5 AlloDerm	155 survivors, died children excluded. 101 primary and 54 patch repair.	Retrospective, survival not named (excluded, no numbers) and length of FU not named.	Recurrence Re-recurrence SBO Subsequent abdominal	Primary 7 % Nonabsorbable 50% vs Biosynthetic 24% Nonabsorbable 67% Biosynthetic 50% Primary 9% Nonabsorbable 17% vs Biosynthetic 21% (ns) Primary 17%

Supplemental Table S6: Surgical morbidity

			operations	Nonabsorbable 67% vs Biosynthetic 48% (ns)
Janssen, 2017(11) 132 CDH, born 2000-2014	132/177 (74.6%) survivors, , 112/132 (84.8%) eligible (because of > 2 year FU)	Retrospective, at least 2 years FU (mean 7.3 years); With/without ECMO and with/without patch evaluated as independent risk factors.	Recurrence SBO Subsequent abdominal surgeries (fundoplication and/or gastrostomy)	7% total patch 14%, primary 4%; 23% after ECMO, 3% without; 20% total patch 29%, primary 16%; 9% after ECMO, 22% without ECMO 11/8% total patch 20%/20%, primary 7%/3% primary 18%/18% after ECMO, 9%/6% without
Criss, 2017(12) 51 CDH, born 2006-2016; 16 open repair, 35 thoracoscopic	?	Retrospective, median FU 2 years (range from 1-102 month)	Recurrence (side not mentioned)	Overall recurrence 13.7%, 6.3% open, 17.1% thoracoscopic
Putnam, 2017(13) 3067 CDH in CDH Registry, 84% open, 16% MIS	?	Retrospective, unclear length of FU or if data are complete	Recurrence SBO	13 % open, 18.4% MIS 19.4% open, 2.3% MIS
Ward, 2017(14) 2379 CDH in Pediatric Health Information System US, born 2009-2016	2379/3051 (78%)survived	Retrospective, comparing preemptive Ladd's procedure or not and occurrence of volvulus	Volvulus	Not significant No Ladd: 6/2259 (0.3%) Ladd: 0%

Supplemental Table S6: Surgical morbidity

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Supplementary Table S7: Musculoskeletal morbidity

Reference (population)	Proportion available at FU	Time frame of FU	Method of outcome evaluation	Outcome scoliosis	Outcome chest wall deformity
Safavi, 2012(1) CDH, born 2005-2007	44/44 Liveborn: 54 Survivors: 44	24-36 mos	Not defined	1/44 (2%)	PE 2/44 (4%)
Rocha, 2012(2) CDH, born 1997-2010	39/39 Survivors: 39	70 mos (4-162)	Not defined	4/39 (10.2%)	PE 6/39 (15.3%)
Kuklova, 2011(3) CDH, born 1996-2009	53/120 Treated: 164 Survived 120 Participated: 53	7 yrs (range not given)	1. PE: clinical evaluation 2. Scoliosis: CA > 5 degrees	14/53(26%)	PE 25/53 (47%) Related to defect
Takayasu, 2016(4) CDH, born 2006-2010	159/182 Born: 674 Survivors: 444 Enrolled 182	4.3 yrs (1.3-7.6)	Not defined	20/159 (12.6%)	PE: 19/159 (11.9%) Chest asymmetry: 12/159 (7.5%)
Jancelewicz, 2013(5) CDH, born 2000-2011	157/160 Treated 187 Survivors: 160 Studied: 157	0.7-12.3 yrs	Scoliosis: clinical evaluation/selected sequential imaging	4/157 (3%) (Only patch pts)	Major chest deformity: 13/157 (8%)
Russell, 2014(6) CDH, born 1989-2012	Chart review of all 279 operated Operated: 279 Survived: 236	0.5 – 23.8 yrs	Clinical evaluation and as reported in chart	25/279 (9%)	59/279 (21%)
Koziarkiewicz, 2014(7) 50 CDH, born?	?	3 mos-18 yrs	Scoliosis: CA>15 degrees	6/50 (12%)	Chest deformity 20/50 (40%) Chest asymmetry 8/50 (16%)

PE: pectus excavatum
CA: Cobb's angle

Supplementary Table S7: Musculoskeletal morbidity

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